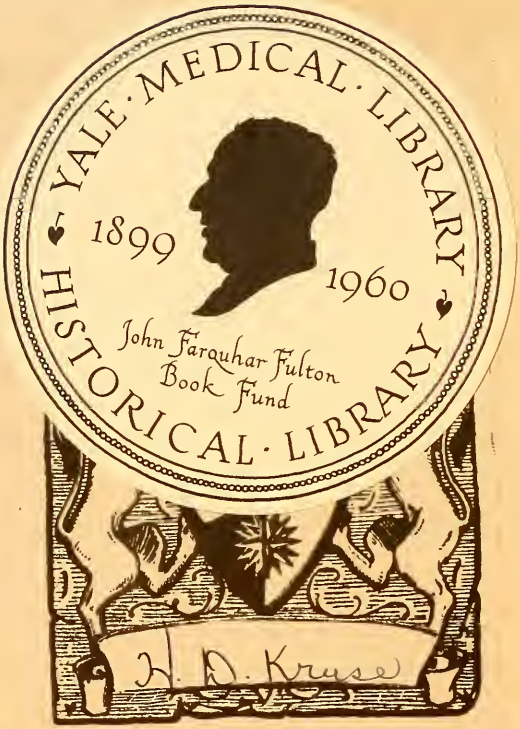
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A TREATISE ON
PELLAGRA

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Gaetano Strombio, the elder, 1782.

The Greatest Pellagraloger.

(From a print in the possession of Professor Sambon.)

A TREATISE ON
PELLAGRA

FOR THE GENERAL PRACTITIONER

BY

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WITH THIRTY-EIGHT ILLUSTRATIONS IN TEXT

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TO THE MEMORY OF MY FATHER

THOMAS F. WOOD, M.D., LL.D.

OF WILMINGTON, NORTH CAROLINA

IN APPRECIATION OF
THE WORK DONE BY HIM FOR HIS NATIVE STATE
IN THE CAUSE OF

PUBLIC HEALTH

PREFACE

The only justification for this book is the fact that when it was begun there was not a single treatise on the subject in the English language except the short articles in Allbutt's System and the Encyclopedia Britannica. The beginning of this book was the translation of Tuczek's "Anatom. und pathologisch. Studien ueber die Pellagra." As this was not a complete discourse on the subject it was necessary to read other works in German, French, and Italian. In the five years that have elapsed the number of these translations has grown and to the knowledge gleaned from these European masters has been added an experience with a large number of cases of the disease. During this period there has been much written on the subject in this country and the study of the disease has been greatly advanced by the establishment of the National Pellagra Conference which meets annually.

It is one of the most interesting chapters in American medical history — this appearance of pellagra. It has been given to few to see the appearance of an entirely unknown disease on virgin soil and to watch the evolution of that disease through all the stages of adaptation to a new field. It has been a study of great sociological as well as medical importance.

The medical profession owes a debt of gratitude to George H. Searcy of Alabama for his splendid work in the first recognition of an outbreak of this disease in the home of the Indian corn. There is also a debt that cannot soon be discharged to J. W. Babcock of South Carolina for his indomitable perseverence in bringing to the attention of the medical profession and the national government the outbreak of the greatest scourge which has yet afflicted the American people; and to him is also due the great credit for the founding of the National Pellagra Conference which is destined to be one of the most important medical and public health organizations in the country.

Through the outbreak of pellagra in the United States many have learned the great importance of that great conservator of human life, the United States Public Health and Marine Hospital Service, while others have for the first time learned to appreciate the greatest medical library in the whole world, that of the Surgeon-General.

It has been attempted in this volume to present an abstract of the literature on the subject for those unfamiliar with foreign languages. None of the chapters are complete but are intended for the use of the general practitioner who wishes an abridged discussion of such a subject. While not a believer in the maize theory, I have tried to present the matter from the standpoint of the zeist as well as the anti-zeist.

The debt which I must acknowledge to other writers and observers is very great. To my teacher, Dr. Joseph Sailer, professor of clinical medicine in the University of Pennsylvania, I am especially indebted for much help and encouragement. To Sir William Osler I wish to express my thanks for help, especially in securing certain Italian publications while in Italy as well as for the wise advice which he is ever ready to extend to the worker in the ranks. To Dr. J. W. Babcock and Dr. C. H. Lavinder I am indebted for many kindnesses as well as for their splendid translation of Marie's "La Pellagra." The bibliography in their work is so thoroughly done that I have deemed a repetition superfluous and I would refer the reader who wishes it to this publication. Much of my work has been done with my colleague, Dr. R. H. Bellamy, who with Dr. John B. Wright was the first in North Carolina to diagnose pellagra; this diagnosis was made before the publication of Searcy's work. Many of my confrères have rendered great service by according me the privilege of studying their instructive and unusual cases of pellagra. Among this number I would especially mention the name of my lamented friend, the late Dr. W. J. H. Bellamy. Among the others are Dr. Thomas M. Green, Dr. John B. Cranmer, and Dr. E. S. Bullock of Wilmington, North Carolina. To Dr. J. K. Averitt of Cedar Creek, North Carolina, and Dr.

Dunlop Thompson I wish also to express my appreciation of their coöperation. The writings of Casal, Gaetano Strombio, the elder, Thiery, Fappolli, Fanzago, Gherardini, Albera, Bona, Allioni, Marzari, Hameau, Brière de Boismont, Balardini, Billod, Landouzy, Bouchard, Lombroso, Tizzoni, Dejerine, Antoniu, Tonnin, Neusser, Baillarger, Tuczek, Belmondo, E. Gaetano Strombio, junior, Pellizzi, Marie, Tirelli, Gosio, Babes, Babes and Sion, Procopiu, Deiaco, Merk, L., Antonini, Triller, Gregor, Nicolas and Jambon in Europe, to which must be added the great work of Professor L. W. Sambon, have been drawn on freely. To Professor Sambon I owe my thanks for many kindnesses and great assistance.

In this country my labors have been greatly lessened by the above-mentioned translation with great additions by Lavinder and Babcock of Marie's "La Pellagra," by the writings of H. F. Harris of Georgia, by the Pellagra Bulletins of the Illinois Board of Health, by the work of Dr. George A. Zeller, by the work of Dr. J. J. Watson, and by the Pellagra Commission of the State of Tennessee.

Dr. H. A. Cotton, superintendent of the New Jersey Hospital for the Insane at Trenton has rendered me great aid with the neuro-pathologic work. For photographs I am indebted to Dr. J. B. Cranmer, Dr. E. S. Bullock, Dr. J. J. Watson, Dr. J. W. Babcock, Dr. C. H. Lavinder, the late Dr. W. J. H. Bellamy, the Illinois Board of Health, the Tennessee Board of Health, the South Carolina Board of Health, and this does not include many others who have aided me by their kindly interest.

Finally, I wish to express my appreciation of the considerate treatment of the publishers who have held up this work for a year on account of a serious sickness from which I only recently recovered.

Edward Jenner Wood.

Wilmington, North Carolina.

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A TREATISE ON PELLAGRA

CHAPTER I

HISTORY AND GEOGRAPHICAL DISTRIBUTION

The importance of a study of the history of a disease in any complete consideration is seldom sufficiently appreciated by the student of the present time. This fact has been explained on the ground that those capable of writing such history are too much occupied with the making of it, and again, the demand for such work is so small that there is not sufficient justification for the expense and labor involved. To Osler we are indebted for a stimulation of this study in this country. He has always emphasized the importance of tracing the disease to the earliest record whenever possible, just as one would study embryology by tracing the ovum through its various stages of development to maturity. Both the error of earlier observation and also that part which has stood the test of time are equally important. In the study of pellagra we are at once confronted with a situation which largely hinges on a correct history of the disease. Since the earliest descriptions the various opinions have been greatly divided regarding the source. Many and, in fact, the majority of writers have contended that it was a disease of comparatively modern times, never observed until early in the eighteenth century. On the other hand there are those equally positive in the opinion that it was a disease known to the ancients and described by them. This latter school considered pellagra a disease which had been mistaken for, or confused with, a number of diseases, chief among which were leprosy and scurvy.

The importance of the history of pellagra is at once appreciated when one remembers that the most important contention of the zeists [1] is that pellagra was unknown in Europe until after the introduction of maize from North America in the latter part of the seventeenth century. Could it be proven that pellagra was a disease of some antiquity known in Europe before the introduction of maize as an article of food, then that food could be declared not to be the cause and thereby open the way for a fairer consideration of the whole problem of the etiology. Certainly, at this time, there can be no problem in medicine, viewed from the standpoint of the southern people, of so much importance. The reader, then, must overlook the rather lengthy discussion of this matter and grant its importance. Certainly, no step in the study of pellagra would be half so important as the disproval of the corn theory in order to make room for a more impartial consideration of the question.

Much may be said regarding the contention which arose during the latter part of the eighteenth century regarding the origin of pellagra and its relationship to such diseases as pellarella, pellarina in Pellano, pellarium, purpura chronica, as well as such diseases as *Mal de la Rosa,* and *Mal del Padrone,* which latter names were only synonyms existing, in some instances, before the word pellagra was coined by the Italian peasantry.

Frapolli and Albera considered pellagra an ancient disease, and the former thought that there was provision made for it in the hospitals since the year 1578. He further stated that some of these cases were called pellarella. Albera considered Sennert's ephelides nothing more nor less than pellagra in a mild form. Strombio, the elder, claimed that there was nothing to the claim of Frapolli regarding pellarella except a similarity of name. Gherardini believed that pellagra was a modern disease and that the name pellarella signified a syphilitic affection. His ground for this belief was that the hospital at Broglio where Frapolli

[1] The word zeist is used throughout this work to indicate an advocate of the theory that damaged or otherwise diseased maize causes pellagra; likewise the term maize will be used always instead of the term Indian corn.

reported his cases of pellarella was only for the treatment of venereal diseases. While Strombio, the elder, was of the opinion that pellagra was a modern disease and that pellarella resembled it in name only, he was skeptical regarding this theory of Gherardini's. Moriggia [1] said that the hospital in Broglio called Hiob was for the purpose of treating venereal diseases and scabies. In Salvator vitale [2] we learn that those suffering with leprosy, cancer, and syphilis were brought to the hospital at Broglio and we infer from the tone of the writer that cases were also admitted with very questionable diagnoses. It would not be unreasonable to suppose that Frapolli had good ground for his belief that among these cases were many of pellagra. Certainly it can be proven that there were many cases admitted that could not be diagnosed as syphilis or venereal disease. It is apparent that if this is the only evidence against the identity of these two diseases it must be dismissed. I have been unable after a thorough search of the literature to find a single other evidence that would tend to prove that these two diseases, pellarella and pellagra, were not identical. It seems reasonable to accept Frapolli's view of the matter unless better evidence of its incorrectness can be brought forward. It is no unusual thing at this time for pellagra to be confused with syphilis, and I know of one case at least where the patient was not satisfied with the diagnosis of pellagra and went to Hot Springs, Arkansas, for treatment and there his condition was accounted specific. If we, in this enlightened time, can make this mistake, it does not seem unreasonable that the same thing should have occurred in the sixteenth century.

Strombio differed with Albera, claiming that pellagra was altogether different from Sennert's ephelides. He said: "The ephelides which the Germans call Sommerbrand appears on the face, the hands, and other parts exposed to the sun's rays. The skin is red in the beginning and then becomes black. The face is not so much spotted as it is altogether changed in color, etc.

[1] Moriggia, "Della Nobilita di Milano."

[2] "Theatrum triumphale Urbis Mediolensis," 1644.

How can one compare this with pellagra?" It would appear according to our present knowledge that such a comparison would be very well founded.

In none of the writings of the ancients was Strombio able to find a complete description of pellagra, but he very aptly remarked that it would not be improbable that the old observers described it in sections, or rather, that the sum total of these various phases would, when united into a whole, make a complete description of the disease. It is comparatively an easy matter to find in ancient works mention of the various symptoms, but it is equally true that none of the earlier writers ever connected them into a whole. Strombio wisely remarked in another place that Hippocrates speaks of more than one kind of pain which "spreads to the neck from the head and from the loins and limbs, of fainting, of coloring of the face, tetanus, melancholia, delirium, and many other conditions which occur in pellagra." It is notable, however, that Hippocrates' description of *sollicitudo* very nearly approaches an accurate description of pellagra. He described such patients as being slightly delirious in the spring, that they avoided the light and companionship of men, and that they seemed terror-stricken by the least sound, and had a dread of seeing their departed friends and ghosts. The connection between this peculiar mental state and the seasonal variation deserves more than a passing mention for there is hardly another disease in which the spring recurrence is so well emphasized.

Gherardini thought that pellagra was a modified form of erysipelas, but Strombio called attention to the fact that this opinion was valueless because the observer merely took into consideration the skin manifestations without any regard to the systemic symptoms. Strombio made a diligent effort to compare pellagra with a number of the diseases described by the ancient writers. He said he was impressed by the old idea that pellagra was merely a remnant of leprosy. This view seemed to have been founded on an opinion of Sauvage's[1] who spoke of *lepra asturiensis* and compared pellagra with different varieties of leprosy. He then

[1] Sauvage, Boissier de' *Nosolog. Met. Ord.*, V, Sp. 4.

studied leprosy as it was known to the Greeks, Arabs, and Jews. He said, further, that he was impressed by his studies that leprosy was a skin disease and that pellagra was a disease in which the skin manifestations were only a small part of an underlying general condition. He next described elephantiasis, but was unable to find any points of similarity with pellagra. Impetigo of Celsus, vitiligo, Alphas, Melas, Leuca of the Greeks, Morphäa Alguada of the Arabs — in none could he find a symptom common to pellagra. He admitted, however, that in many of the descriptions of leprosy of the Jews, if considered in the same broad sense as Hippocrates wrote, he was able to find symptoms differing little from those characteristic of pellagra. In that time leprosy must have been a broad term subject to great flexibility and under this term were included many different skin diseases which have since been separately described.

It seems remarkable how many writers confused pellagra and scurvy. Strombio said that no other disease so closely resembled pellagra and pointed out that the filthy and unhygienic manner of living of the peasantry predisposed to both. Further he said that general exhaustion, diarrhœa, fever, and vagabond pains were common to both conditions. He thought that scurvy was favored by moist air and dampness, while pellagra usually occurred in the hill country. It seems strange that after a century and a half Sambon should again emphasize this fact in his effort to work out the etiology from the standpoint of the geographical peculiarities. This observer employs the fact that pellagra occurs more commonly in the hill country to prove his contention that the disease is transmitted by the intermediate host, the Simulium reptans, which lays its eggs only in rapidly running water, hence requiring the higher regions.

In one place Sauvage gave the name *lepra scorbutica* to the disease *Mal de la Rosa,* but he did not consider it a genuine scurvy because in his opinion *Mal de la Rosa* was an incurable disease while scurvy was comparatively trivial.

Because of the nervous manifestations an effort was made to compare pellagra with hypochondriasis, but in spite of the weak-

ness, pains, fainting, melancholia, and even dementia there were sufficient distinguishing characteristics manifested to differentiate readily the two conditions even in the earlier days.

Astruc said of pellarella: "It does not differ in many manifestations from our scorbutic pellagra." But he described the disease as affecting the palms of the hands and the soles of the feet with a pus formation and much furrowing of the skin. Strombio thought pellagra might as well be compared with syphilis, and he further scoffed at the idea of Videmar that it was an old skin lesion on the ground that the natural conditions of man were the same and had undergone no change, and further that hypochondriasis was an old condition. But Strombio pointed out the fact that hypochondriasis was by no means peculiar to pellagra.

Bona thought it was an old disease akin to elephantiasis which had undergone great evolutionary change. Videmar mistook a disease called *solsido* by the country people for pellagra, but this was probably an error, as it was a very trivial condition, thereby differing from pellagra. Allioni took Strombio to task for concluding so positively that there was no connection between his purpura chronica and pellagra.

It is likely that our present idea of the modernity of pellagra owes its origin largely to the writings of the above oft-mentioned Gaetno Strombio. It is only right that the work of this man should be given most respectful attention, for he wrought valiantly in his day and time. His writings show great accuracy and a wonderful power of observation, entitling them to favorable comment as accurate scientific work, even by the fierce light of modern criticism. Probably no man before or since his time was given such opportunities for the study of the disease. In 1784 the first hospital for the treatment of pellagra was established under a grant of Joseph II of Austria, and Strombio was placed in charge of it. At the close of 1788 this hospital was abandoned and Strombio was given charge of the greater hospital of the same character in Milan. This position was held for three years, and during that time his observations were made. He

mentioned the fact that his observations were on a sufficiently large number of cases to entitle him to arrive at logical conclusions. It is important to weigh Strombio's conclusions with great care. We naturally conclude that he was prejudiced and could see the matter from the one standpoint, — that of a modern disease. On the other hand we should consider that in the more recent history of pellagra it is a notable fact that wherever it makes its first appearance there it is, for a time at least, considered a new disease, and many fantastic names have been coined to designate it, as psilosis pigmentosa [1] in Barbadoes. Even in the United States many physicians refused to acknowledge that the disease appearing in almost epidemic form in certain sections about the year 1905 was pellagra. I count myself among the number of those who refused to consider this disease under its proper name for a long time after its first appearance. We note the statement of Strombio that in the pellagra contest of the National Society of Milan the thesis of Videmar was not published. This thesis was entitled "Nil novum sub sole." Like this writer, there have been observers in every generation who would not accept the idea that pellagra was a new disease. From what has been said above one would infer that there is good ground for the idea that pellagra was an old disease which could readily have been confused with a number of other diseases or conditions, and further, that if in this enlightened time when medical literature has added so much to the physician's armamentarium there is still so often doubt of the diagnosis, it would be only fair to presume the occurrence of error in the earlier times.

In 1735 a physician of Oviedo, Gaspar Casal, who is designated as *protomedicin de Castille* by Roussel and also as physician to Philip V, described a condition among the poor inhabitants of the country which he called "a kind of leprosy, very singular." This first observation was made on eight cases under date of March 26. He never used the term pellagra, which was coined probably years later, but always *Mal de la Rosa,* though I have

[1] Trans. Pan-American Medical Congress, 1893.

never found evidence that he considered this name to have been coined by him. The Italian and French physicians did not accept the idea until 1845 that the disease described by Casal was the same as that described by Frapolli and called by him pellagra. This latter observation was made in Lombardy thirty-six years later. The idea of the identity of pellagra and *Mal de la Rosa* was never seriously contested according to Roussel, who stated that his idea of the unity of the two diseases was borne out by the unanimous assent of the Spanish physicians in 1847 and likewise by the Academy of Medicine in 1849.

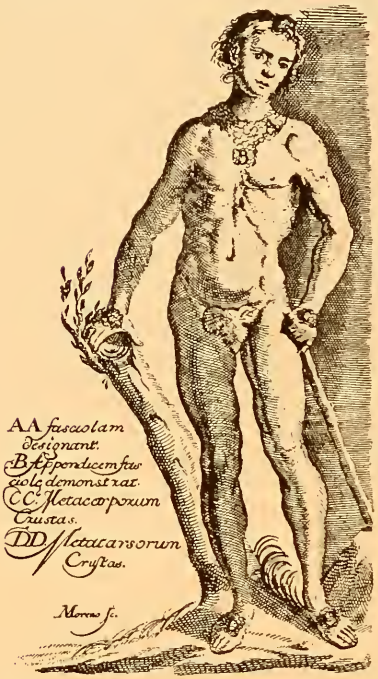

FIG. 1. — CASAL'S IDEA OF THE DISTRIBUTION OF THE SKIN LESION IN PELLAGRA.

The Academy of Sciences in August, 1847, formulated the query, "Spanish pellagra called *Mal de la Rosa,* is it not a form of pellagra?"

The volume in which are found Casal's records was written in Spanish, but the medical portion is in Latin.[1] Roussel said that this work was so little known out of Spain that in 1843 he was the first to consider the question of the identity of Casal's *Mal de la Rosa* with Italian

[1] "Præ vernaculis aliis affectionibus dominatrix merito regionis hujus scabies appellari debet. . . . Secundus, a scabie, endemicus morbus est lepra. . . . His adhibere possumus malignum quamdam lepræ speciem, quæ singularissima est, et hic patrio vocabulo, Mal de la Rose, nuncupatur. . . . Cum videssem nullam vernacularum affectionum horribiliorem, contumacioremque, non abs re fore putavi me historiam scribere." — "Historia natural y medica de el Principado de Asturias," Abra posthuma del Doctor D. G. Casal, Medico de Su Magestad y su Protomedicin de Castilla, Madrid, 1762. Edited by Juan Garcia Sevillano. There recently appeared a new edition of Casal's work. The medical portion, which was originally written in Latin, in this edition is in Spanish.

pellagra. This claim was substantiated by Thounel, Strombio, Cerri, and Marzari, but none of these observers so well appreciated this fact as did Royer in 1834.

Roussel [1] made his report to the Academy of Medicine in 1849, giving the result of a voyage of medical inspection of seven months' duration. He made twenty-two observations in the same territory in which Casal's work was done and stated even more positively than formerly the correctness of his original opinion. He stated that there could no longer be any doubt on the question of the identity of pellagra and *Mal de la Rosa* and explained the late recognition of this fact on the ground, mentioned above, that Casal's work was so little known out of the territory in which his observations were made. This is illustrated in the writings of Thiery,[2] published in 1755 in the *Journal de Vandermonde*. This writer was at that time a regent of the Faculty of Paris and had been an ambassador of Louis XV in Madrid and at that time had known Casal at the court of Philip V. He made careful notes of his recollections of these interviews and also of his reading of Casal's manuscripts, and this record forms a valuable chapter in the history of the disease because it helps to fix the date of Casal's writings, which has been disputed by some who have claimed that he did not make his observations as soon as 1735. Thiery's "Notice" became celebrated. It was an abstract of an address delivered to Chomel, dean of the Faculty of Paris. In his writings he called the attention of the medical world to pellagrous erythema observed, according to him, in the Asturias. At this same time the disease was described in Italy by Pujati and Jacopo Odoardi [3] in the Venetian states, where it was known as Alpine scurvy. In the same year Lombardy was ravaged by pellagra. Soon after this Sauvage in his outline of

[1] Roussel, "Rapport transmis à l'Académie de Medicine, par M. le ministre de l'agriculture, du commerce et des travaux publics, le 27 février, 1849." *Bulletin de l'Académie*, t. XIV, p. 572.

[2] Thiery, "Rec. période. de méd. et de chir." Paris, 1755, t. II, p. 337.

[3] "Contribution à l'étude de la Pellagre et du Syndrome pellagreux," par MM. J. Nicolas et A. Jambon. (Clinique des Maladies cutanées et vénériennes de l'Antiquaille de Lyon.) *Annales de Dermatologie et de Syphilographie*, 1908, 4. Série, p. 385.

"Nosologie méthodique" attempted to place *Mal de la Rosa* under the name *lepra asturiensis* as the fourth species in the genus *lepra* in the group of *cachexias.*

Thirty years after this an Englishman, Dr. Townsend, traveling in Casal's territory, made some observations on pellagra which he had noted. He visited the hospital at Oviedo and was given all the information available by the physicians, Antonio Durand and Francisco Nova. This information, according to Roussel, was of little importance. This latter writer made a thorough search of Spanish literature in an effort to determine if the disease described by Casal and later mentioned by Townsend had disappeared from Spain. He was able to discover only that the celebrated writer, Feijoo, in a letter written to Casal under date of December 2, 1740, announced that *Mal de la Rosa* existed in Galicia, his native country. He further wrote that Dr. Batalla of Santiago in 1859 had said that sufficient importance had not been accorded to the opinion expressed in a work entitled "Teatro Critico." I have not been able to secure a reading of this work, but presume from Roussel's writing that this was another account of pellagra in Spain which had never attracted any attention. According to Roussel's research there were no writings in Spanish from the time of Casal's account to the year 1826, when an article appeared in the Barcelona *Journal de Médicine,* which mentioned the existence of pellagra in the environs of Alcaniz in Aragon. Either pellagra did not exist in Spain during this period or else it was omitted in all medical writings. In 1846 Roussel appealed to Professor Orfila, who made inquiry of one Dr. Gonzales Crespo of Guadalajara, who in turn stated that nothing had been published on the subject since the posthumous work of Casal in 1762, and further, that the existence of *Mal de la Rosa* had not been noted out of the Asturias.

Dr. Gimeno wrote to Hijar of the district of Alcaniz under date of October 22, 1826, the following letter, which was published in the *Diario General de las Ciencias Medicas* at Barcelona:

"Since I have finished my studies and established myself in this country to practice medicine I was surprised regarding this

affection which I wish to describe. The cause of the chronicity, of the complexity of the symptoms, and still more of the incurability made me consult the few books that I had and the old physicians of the neighborhood; I did not find any light. Only in the dictionary of Boliano, under the name *Mal de la Rosa* of the fourth species of the genus *lepra,* was I able to find any reference. I find something analogous with regard to the intermittance and of the same type; but in the remaining symptoms they differed sufficiently to distinguish them. Above all I was not satisfied with the plan of treatment.

"In October, 1820, I addressed a circular to six physicians of the neighborhood. Of those who replied to me their descriptions conformed to my own. . . . The disease described under the name pellagra resembles more or less and is analogous to that which I have mentioned in the history sent you. This history was the result of only one hundred observations in the space of eleven years. With regard to the nature of the disease I am of the opinion of the other writers that it is a chronic gastroenteritis added to a disturbance of the hepatic system. The liver was found in a state of phlegmasia, but a phlegmasia *sui generis,* distinct from the others."

The descriptive document annexed to the letter of Dr. Gimeno bore the title "Histoire ou description de la maladie vulgairement appelée *Mal del Higado.*" This latter name indicated a disease of the liver. The author described a disease which was common to a large number of inhabitants of the villages (pueblos) of the district of Alcaniz and of some of those of Daroca, Terruel, and Morella. He claimed that it was hereditary but not contagious. "It could not be considered endemic," said Gimeno, "on account of the diversity of the situation, of the temperature, of the soil, and of the locations where it occurred."

In 1847 Mendez-Alvaro [1] wrote that in November, 1835, he

[1] Mendez-Alvaro, *Boletin de medicina* no du, 2 Septembre, 1847. "Noticia sobre la pelagra el doc. D. F. Mendez-Alvaro."

noted in Villamajor de Santiago, a province of Guenca, a number of people who had a skin lesion on the backs of the hands and anterior surfaces of the forearms which was characterized by small scales producing a cooked appearance of the inflamed skin. The skin was thickened and itched slightly. The first patients were females who were very poor. These people used a form of lye which was a substitute for soap. It was thought that this caused the disease, but the writer soon disproved this theory by finding the disease in men as well as in women. He further noted that these patients were often delirious and the disease was followed by a sort of dementia which they called *flema salada.* In the months of January and February, 1836, he saw several patients with vertigo and cerebral symptoms which were thought to be secondary to the skin affection. One of the patients died and a large number had cutaneous desquamation, especially on the arms and hands. The description of *Mal de la Rosa* by Casal did not give a complete picture of the condition, but the writer was impressed by the analogy, especially when he took into consideration the nervous and gastrointestinal symptoms. It was finally decided that the two conditions were one and the same.

This report of Mendez-Alvaro is the first record of the disease *flema salada,* which must have been pellagra, though the eighteen years of its observation left no very accurate account of it, and after this period had elapsed the disease seems to have disappeared, due, in all probability, to the better knowledge of pellagra whereby the diseases were shown to be identical. There were three Asturian physicians to follow up this work of Mendez-Alvara. One of these was a physician of the province of Leon, Juan Andrez Enriques of Fermoselle, who described the occurrence of *flema salada* between the Duoro and Tormes rivers. He was unable to find any record of a similar condition in any of the medical authors of that day, though he found several symptoms that suggested *Mal de la Rosa.* This writer dismissed the matter without any great amount of study, hoping that time would clear up the mystery, though he resented bitterly the coming of foreigners to help out the sufficiently wise Spanish physicians.

At the same time this observer spoke of *Mal del Monte,* which in all probability was pellagra. It affected both sexes alike and occurred only in the poor. It was supposed to be hereditary and was always chronic. Its duration was indefinite and it often lasted throughout life, the patient in some cases reaching a great age. He described it as affecting the skin of the backs of the hands up to the middle of the forearm. The skin became almost transparent, shiny, and parchment-like. The patients had vertigo, illusions, and often an intermittent dementia. The country people spoke of it as *Mal del Monte* or *Mal el Monte.* In the section where this condition was found were a number of unfortunates who, though previously healthy, became emaciated and depressed. The face became sad and the expression fixed. The words were always enunciated very slowly. The patients were usually emotional. At times there were skin disturbances, which suggested burns and for which the disease was often mistaken. It is interesting to note that this same mistake has been made in this country in recent years before the existence of pellagra had been recognized, and many attendants in institutions have unjustly lost their positions on account of the authorities supposing that the skin lesion of pellagra was a burn caused by carelessness in giving too hot a bath. This condition was further described as causing a slow movement of the limbs, a mental action which was retarded, suggesting that the mind was laboring heavily when considering the simplest things, and an unwillingness to take food necessitating the actual placing of food in the mouth. There was no taste and no desire for food. The sphincters finally became relaxed and the patient died in a condition of dementia. It was an accepted idea that the disease was incurable. The writer concluded his report thus: "I beg the physicians of the Asturias and other places where this disease occurs to publish the histories of their cases in order to determine if the disease is the same and to find out some curative measure which will give better results in rescuing these poor victims from a deplorable death."

Insufficient as was this publication, Roussel remarked that

Enriquez by it made known the fact of the existence of a pellagrous or pellagroid epidemic in the province of Zamora near the frontier of the Portugese province of Tras os Monte.

Of the Asturian physicians who responded to the appeal of the Madrid journal, Higino del Campo took first prize. In an article in the *Boletin de Medicina* for October 10, 1847, under the title of "The Value of Sea Water," he extolled sea water in the treatment of *Mal de la Rosa*. The Spaniards found much fault with the writings of Del Campo, but in spite of the unjust criticism of Casal and in spite of the faulty idea that in the blood of the pellagrin there was an accumulation of heat, his work was valuable because it showed the disease as it was found in the Asturias and indicated careful study and observation.

Del Campo thought that there was a difference between the so-called *Calor del Higado* and the disease described by Casal. He said: "I have never observed those traces of rough and shining cicatrices which Casal considered pathognomonic." A great deal of heated comment among the Spaniards was caused by this criticism of their idol, Casal. Roussel well said that Del Campo seemed to disregard the stage of the skin lesion, as it is a well recognized fact that at the various stages of the skin manifestation there is a decided difference in the character and general appearance. Antonio del Valle objected to this criticism of Del Campo because there was no mention by this latter observer that at one stage the skin areas affected were dark red without exfoliation, that the appearance was of a shining brilliance resembling the marks made by burns. He was confident that *Mal de la Rosa* and *Calor del Higado* were a single disease. After a pompous eulogy of Casal he spoke of the frequency of the disease, claiming that there was in the Asturias one such case to every six hundred inhabitants, but it was otherwise estimated that there was one to every three or four hundred.

Valle said that the disease was a chronic affection of an exanthematous form, though often squamous, of a dark rose color; that it occurred by predilection on the parts exposed to the sun's rays, especially on the metacarpal and metatarsal portions, though

sometimes on the lateral portions of the neck and the superior and anterior parts of the chest. It developed with all its intensity in spring with the coming of hot weather. It was constantly preceded and accompanied by profound functional disturbances. The cerebral manifestations, according to him, were more than the digestive. The symptoms, especially of the skin, decreased with the approach of winter. The skin where occurred the erythema was described as having a dull rose red color without any desquamation, appearing much like the traces left by a burn. The chief nervous disturbances were given as slight vertigo and other trivial nervous affections which, when they became severe, presented conditions most difficult to treat. He said: "If this affection is called pellagra, there can be no doubt that in those old principalities, where a condition from time immemorial has been called *Mal de la Rosa* and *Mal del Higado*, is true pellagra, inasmuch as it embraces all these conditions." He further said that if the word pellagra, according to its Italian meaning, signified fissures or erosions of the skin, it agreed with *Mal de la Rosa* or Asturian pellagra, for it occurred in the same manner as had been described by Casal, who was spoken of as the "Hippocrates of the Asturias." *Profundis sæpissime intercisam fissuris ad vivam asque carnem penetrantibus.*

Roussel analyzed the writings of several Spanish physicians under the title "La Pellagra y Mal de la Rosa," and made the following synopsis:

(1) That pellagra up to the year 1847 had received no careful study in Spain; that no part of it had received careful observation sufficient to furnish a reliable description or consideration of the etiology.

(2) That beyond the endemic pellagra of the Asturias there existed other identical endemics which so nearly resembled it that in the state of the knowledge of the disease it was very difficult to designate them under other names.

(3) That the endemic pellagroid or pellagrous districts were found in a large number of places far distant from each other. The disease occurred in the north and also in the central part of

Spain. From 1820 to 1826 one of these outbreaks went by the name *Mal del Higado* and occurred in Aragon, in many places in the province of Terruel, in the river valley of the Ebre, in the basin of the Gaudeloupe, and in the environs of Alcaniz and on the borders of Xiloca in the environs of Daroca. In 1835 there was recognized a strange malady under the name *flema salada* in the upper basin of the Guadiana, in the province of Guenca, in New Castile, and possibly in other places. In 1847 an endemic occurred under the name *Mal del Monte* or *Mal el Monte* near the frontier of Portugal, in the basin of the Dauro, and in the province of Zamora. There also occurred *Mal de la Rosa* in the Asturias where Casal first found it. It extended from the coast between Aviles and Gijon to the foot of the mountains.

(4) It is granted that all these endemics, however imperfectly studied, have the appearance of Pellagra, which in Spain, according to geographical, topographical, and climatic reports, together with certain points of variation, presents a general similarity of such a nature that the unity of the disease cannot be doubted. In all cases it was found to occur in country people and in workers in the earth, and especially in the very poor.

In 1859 Batalla called attention in the *Siglio Medico* to the fact of the reported observation of Feijoo, which was made in 1740. He also showed the correctness of this report which related the presence of *Mal de la Rosa* in Galicia. This observation was based on sixty-four cases, but the object of the paper seemed more for extolling the virtue of sulphur baths in the treatment. Batalla found the disease essentially in middle life and more common in men than in women, and he further noted the important fact that all of his cases were from the country districts and were poor people. The disease was attributed to poor maize. In the clinical description there was no difference from that of the Italians of the same period. His idea of the etiology caused disagreement among his confrères. This opposition came from the mountainous regions of Castile and Aragon where Mendez-Alvaro had observed it under the name *flema salada* in 1835.

This latter condition was spoken of as *Mal de la Rosa,* with some slight variations which had resulted from climate and other circumstances. In the journal *Siglio Medico* were published from Perrote de Villahoz, Marti, de Villarejo, de Salvanes, and Calmarza announcements that pellagra under the name *flema salada* was endemic in their practices and among those who did not use maize. Roussel, to whom I am indebted for practically all this information regarding the history of these various endemics under many names, but always of true pellagra, takes Batalla to task for what he called his many contradictions. This was evidently due to the one fact that Batalla had the courage to describe pellagra in those patients who had never eaten maize. Had all the observers had the courage of this man the etiology would have had much better chance of being settled.

Costallat denied the identity of the two endemics, but Roussel thought that he did not establish his position by good descriptions of the condition nor on any evidence of detailed observation. Because of this objection which had arisen in Spain Costallat went through the Pyrenees and arrived in June, 1860, at Villahoz and Mahamud. This excursion of medical investigation was described in two articles. One of these was a letter to Landouzy which he entitled "Pellagra and Acrodynia," and this was followed by an article in Spanish under the title "The Disease Known in Spain under the Name *Flema Salada* Is Not Pellagra," which bore the date of 1861. He considered the disease merely as acrodynia in an endemic condition. He summed up the differential diagnosis in the ten following points:

(1) The erythema is more pronounced but more definitely circumscribed on the hands and feet. A patient was mentioned who had been sick for eighteen months and had the erythema in the space between the first and second metacarpal bones. The lesion had acquired the character of a superficial ulcer surrounded by scales and thick scabs. Costallat observed that nothing of this kind was ever observed in pellagra.

(2) A peculiar sensation in the plantar surface of the feet when the patient walked, which is compared to walking on cobble

stones. This phenomenon Costallat said that he mentioned regarding the epidemic of Paris (acrodynia).

(3) A dark color of the skin of the wrists, the feet, the arms, the thighs, and also of the body was mentioned and described as a chocolate color. The writer never saw anything like it in pellagra.

(4) None of the patients had the characteristically furrowed tongue of pellagra.

(5) From Perrote Costallat learned of a sign to which he seemed to attach considerable importance: a swelling of the conjunctivæ with lacrimation.

(6) He thought that formication was more a symptom of acrodynia than of pellagra, and mentioned its occurrence in this series of cases and said that the trouble was confined to the hands and feet.

(7) Paraplegia was counted a differential point of moment. It was claimed to be more often present in *flema salada* than in pellagra. It affected more commonly the lower extremities and was an indication for a grave prognosis.

(8) Costallat found the age of the patient an argument for his diagnosis. His youngest affected with pellagra was five years, while Perrote's youngest was forty-four.

(9) Perrote never saw in acrodynia suicide nor even a tendency to it. Costallat refers to suicides in pellagra occurring especially in Lombardy.

(10) Acrodynia is much more rapid in its course than pellagra.

Roussel concluded that the question of the identity of *flema salada* was the most obscure and interesting point in the history of pellagra in Spain. The question at that time seemed to have been how could pellagra occur without the eating of maize. Had the victims of *flema salada* presented the history of maize consumption it is hardly probable that this difficulty would have arisen. It is a notable fact that in recent years when nearly every writer has espoused the maize theory of Lombroso little or no mention has been made of this condition which caused so

much contention in the time of Costallat. This latter writer thought that errors in cultivation, especially an absence of lime in the soil, rendered the cereal subject to alterations, and as a result there occurred a disease which seemed to be acrodynia or what he called "cereal convulsion" occurring in epidemic form.

It is altogether probable that acrodynia has in some instances been confused with pellagra in this country, and I have in mind a case described to me by one of my confrères who thought it was a case of pellagra. It is no less a difficult differential diagnosis at this present time.

As before stated, Gaetano Strombio was the first of the Italians to describe pellagra, and probably no work since that time has added materially to the account which he gave.

Sixteen years after the description of Casal the "Notice" of Thiery was published under the name *Mal de la Rosa.* Simultaneously in many parts of Italy there appeared reports of the same condition. A physician of the Hospital Majeur of Milan, Francisco Frapolli, in 1771 published an important work entitled "Animadversiones in morbum vulgo pelagram." Four years after this a physician of Cannobia, Francisco Zanetti, mentioned the appearance of the disease on the shores of the Lago Maggiori and refers to it thus: "Nemo quem ipse sciam usque adhuc de haec cutis affectione peculiariter scripsit." He said that the disease was vulgarly called pellagra and affected chiefly the poor and malnourished. In 1776 a physician of Bellune, Jacopo Odoardi, wrote of a form of scurvy which he designated *scorbuto alpino.* Antonio Pujati, a professor in the university at Padua, described the disease under the names *pellarina, scottura di sole, calore del fegato, mal della spienza.* He considered it a special kind of scurvy occurring in the sub-alpine region.

In 1780 Michel Gherardini, a physician of the Hospital Majeur of Milan as Frapolli had been, wrote an account which was the best that had appeared up to that date. About this same time Albera's work appeared, as has been mentioned on a previous page. At the time it caused considerable comment and has left the name indelibly connected with the early history of the disease.

Roussel referred to this work of Albera's as being *mystico-scientifique.* Albera spoke of a disease caused by insolation, which he said was vulgarly called pellagra.

In 1791 Sartago described *scorbuto montano,* occurring in the territory of Aviano. It was found to conform to the general description of Strombio. At about this same time Allioni first recognized the malady in Piedmont.

In 1810 Marzari published his work entitled "Essai Medico-politique," in which he said that he had recognized pellagra in practically all the new provinces which Napoleon had created beyond the Alps. It was this same Marzari who first gave impetus to the maize theory of the etiology, although this view had been advocated by Strombio and others of the same period many years before. He laid particular stress on the fact that polenta was consumed in great quantities by the Italian peasantry and that they ate no meat or other kind of food. He was of the opinion that maize was one of the chief causes, but we note that he does not look on it as a specific; it appears that he merely counted it as one of the evidences of poor hygienic conditions. This same writer discussed at considerable length the chemistry of maize. His experience was drawn from twenty years' study of the disease as he found it in the country of Trevisan. Roussel considered the work of this man to have been of inestimable value because of his clear advocacy of the damaged maize theory of the etiology.

From this time the history of pellagra in Italy is the history of the development of the maize theory. It is to be regretted that some of this energy could not have been directed to the study of the clinical manifestations of the disease. Though the Italians had all the clinical material needed, practically no progress was made along this line after the work of the elder Strombio whose writing has been mentioned frequently.

Roussel is author of the statement that Professor Franzago inserted in his "Memoire," published in 1815, a reclamation of his previous opinion regarding the etiology and his acceptance of the maize theory. He said:

"I take this occasion to inform my readers of the opinion of a recent writer on this question. Doctor Guerreschi in his 'Observations sur la pellagra,' published in the *Journal of Parma,* is certain that *melica* (a name signifying maize) is the true and only cause of pellagra and he expressed the hope that henceforth pellagra be called *Raphania maistica.* He noted that the numerous and varied causes given in the past were not sufficient to produce the disease. He then spoke of the bread called milange, which in the past had been in general use. It was composed of wheat flour, of beans, of German wheat or spelt, of rye, and added that at the time of his writing maize and maize alone had taken the place of this compound food entirely. Wheat had become a rare plant. . . . He said that all the pellagrins whom he had examined replied in the affirmative when asked if they ate polenta and further declared that it was their only food."

About twelve years before this time Thouvenel had called attention to a new malady which he thought at that time might be readily eradicated. Marzari said that the only way to rid Italy from the ravages of pellagra was to supply the poor with bread made of wheat, meat, and potatoes, but to teach the peasantry the importance of such a change in their manner of living he was unable to do.

In 1787 a young Frenchman, Lavacher de la Feutrie, followed Jansen and Hollen-Hagen in the study of pellagra. He studied the disease in Lombardy, and about the year 1802 communicated to the Société Médicale d'Émulation the results. In 1806 it was made a special publication. There was no further reference in the French medical literature until 1829 when Brière de Boismont made his observation, although there was abundant opportunity for the study of the disease. There was, however, one case of a French soldier observed by Husson in the Hôtel Dieu and later by Alibert in the Hospital Saint Louis. This case did not attract as much attention as its importance deserved. Biett, who had observed pellagra in Italy, did not make the careful study at this time that did Alibert, who classified it as a dermatosis.

Two articles of merit were published at this time in France. One was "L'Article Pellagra," published in 1819 by Jourdan in the *Dictionnaire des Sciences Médicales.* The other was a report on *Mal del Higado* by Dr. Gimeno in 1826. He identified this condition, which was found in Alcaniz to be the same as the pellagra of Italy. Still another important work was published in 1834 by Rayer.

The work of Brière de Boismont was published in 1830 after its presentation to the Academy of Science and was of the greatest importance, because it called attention to the fact that within a few miles of Paris the disease occurred in the thousands, and he complained that there had not been enough attention paid to the matter by the medical profession. There were others to add their testimony to the correctness of his claim regarding the prevalence throughout France. At this same time the malady appeared unrecognized in the southwest portion of Italy. It had already been noted in 1829 that the disease was attacking the poorer classes in the lower parts of Arcachon, and the fact of the identity of this disease with Italian pellagra had been already mentioned by several physicians in Bordeaux. In spite of this report the medical profession of this section had not been interested and even the physicians of Paris, among which number was Brière de Boismont, had not paid the matter the slightest attention. There were a few, however, who did study the disease at this period in the face of this general apathy of the profession, and they deserve particular reference. Among this number the most important contributor was Hameau,[1] whose writings have always been counted of the greatest importance.

In 1818 this physician of Teste de Buch, Dr. Hameau, had under his care a woman whom the physicians considered was suffering from an obstruction of the bowels. The patient was markedly malnourished. She had three daughters in good health.

[1] Hameau, J. M. G.. "Une maladie peu connue observée (en 1818) dans les environs de la Teste." Soc. Royale de Med. de Bordeaux, 1829. *Jour. de Méd. de Bordeaux,* 1829, *Bull. de l'Acad. de Méd.*, 1832. — "Description d'une maladie nouvelle observée sur le littoral du bassin d'Arachon." *Bull. Acad. de Méd.*, Paris, 1837–1838. — "De la Pellagra," 1853.

In 1819 he was called to the same house to see the youngest daughter, who was affected similarly to the mother. Soon after this patient appeared cured. In June, 1820, however, she returned to Hameau and reported that for one month she had suffered a return of the former symptoms. In 1821 he was called the third time to attend this same patient, whom he found in a serious state. She died in February, 1824. In his work in this neighborhood Hameau was constantly reminded of this case by numerous repetitions of the same symptom complex. He was of the opinion that the same condition existed over a much larger territory than the field of his observation, and he was impressed with the gravity of it. In 1824 (May) he acquired a new case from a farming community and he noted what he considered a remarkable condition, two cases in one family. His records show numerous cases and his description indicates the carefulness of his observation. In 1829, before the Royal Society of Bordeaux, he presented a report on "a disease little known which was occurring in the environs of Teste." He described it as a disease of the skin about which the literature had little to say. This disease was menacing the country from which he came and he wished to mention the chief symptoms in the hope that he would be able to secure some aid in giving relief to the unfortunate victims. This writing was published in the *Journal de Médecine Pratique* of Bordeaux, and the Society of Medicine invited a conference of the physicians interested to consider the matter. The secretary, Dupuch-Lapointe, reported that Hameau presented many of the phenomena which the Italians had described as occurring in pellagra and it was the opinion that there was an analogy between the two conditions. Gintrac and Bonnet went a step further and declared the two conditions identical. All the facts in the case were developed in Hameau's second work, the "Memoire," which, while an important work, attracted only local attention. Following this the disease was recognized in the district of Brazas. A young physician of the Teste, Lalesque, studied it further and wrote a monograph, which he addressed to the Council of Health of Bordeaux. Soon after this the physicians

of the Landes, Ardusset and Beyris, proved the identity of this condition and Lombardian pellagra. From this time the term *maladie de la Teste* was supplanted by the better term *pellagra des Landes.*

The extent of the disease as well as the gravity soon alarmed the authorities of the Gironde and they selected Leon Marchand, the physician in charge of infectious diseases, to make a new and more complete study. This action was confirmed by the Minister of Agriculture and Commerce in 1836. Many years were devoted to this work, and in 1843 he wrote a monograph for the Paris Academy of Medicine in which the number of cases was estimated at one hundred in the district of Linx. He found that Hameau had made his observations on seventy-six cases and further that these patients were country people, especially workers in the earth and shepherds. Not only did he find it in the poor, but also in better conditioned people. He found, however, that the victim was always poorly nourished. From 1836 to 1842 Marchand found pellagra in all of the twenty communes of the Gironde. It was noted at this time that it was a disease not occurring in the cities. There was only very rarely a case in Bordeaux. Roussel mentioned that in the hospital Saint André with seven hundred patients there was only one case of pellagra. It was found that in at least one instance the disease was confused with Pompholix diutinus.

When Billod [1] made his observation on the disease which was known as pseudo-pellagra, the first tangible objection to the maize theory was formulated, for the only difference between pseudo-pellagra and pellagra was that in the former no maize was eaten, while the reverse was true of the latter. The question was asked: "Is this variety of pellagra described by Billod in the insane to be considered as pellagra?" Roussel thought not and gave as his reasons that the disease occurred in people who had not eaten corn and in sections where it was not known. It would have been more scientific if this distinguished pellagrologer had reasoned

[1] Rapport de l'épédemie de Sainte-Gemmes avec la pseudo-pellagra de Billod et de Beri-beri. Paris Thesis, 1899, by J. Martin.

forward instead of backward. It is likely that much of the subsequent confusion would have been avoided and while the question might have remained unsolved, the true solution would have been much more likely. I have studied the case reports of Billod carefully and am convinced that if this disease was not pellagra, then pellagra does not occur in the United States and we have fallen into a great error. Billod's description is exactly the same as the description of the disease known as pellagra in the southern states and is the same pellagra which Babcock and Williams observed in Italy recently and found to be the same as the disease in South Carolina.

Gintrac wrote, according to Roussel, the following: "The maize which is collected in the Landes de Gascogne is carried to Teste where it is consumed; it is frequently damaged. Hameau found in the granaries a large quantity of *verderame,* but in spite of this fact not a single case of pellagra has been observed in Teste." On the other hand Costallat said that he had never observed a case in which a definite history of maize consumption was not obtainable.

Lemaire, the health officer of Minizan, who had observed the disease for many years, regarded it as peculiar to the section and affecting country people. He said that it was known among the peasantry as *mal d'Aerouse,* but the description caused Roussel to doubt the correctness of the diagnosis, as there was evidence to show that two diseases were confused. These two were pellagra and a palmar psoriasis, and again there was another condition which was a fusion of the two. Pellagra was found not only under the name *mal d'Aerouse*, but also as *mal de Bascons*, *mal de Saint Amans,* and *mal de Sainte-Rosa. Mal de Saint Amans* was derived from a statue in Bascons to Saint Amans which was always damp and sweating and this sweat was collected to be applied as a remedy to the affected part. It was thought by some that the term was a corruption of *mal des Saintes-Mains* and had nothing to do with the statue to Saint Amans. This name was supposed to owe its origin to the fact of the prevalence of the skin lesion on the backs of the hands.

The name *mal de Sainte-Rosa* was derived from a fountain of muddy water which existed at Ichoux and which was dedicated to Saint Rose. The water was supposed to have a curative effect on pellagrins.

In 1846 Lachaise wrote of the presence of pellagra in the form of an epidemic in Pologne in Roumania and attributed it to the introduction from abroad of bad maize.

In 1858 Julius Theodori reported the occurrence of the disease in the provinces of the Danube. But it is interesting to note in this connection that in 1847 Caillet had written that he did not think pellagra occurred in the provinces of the Danube, but he found in Moldavia "a new disease," which was designated *lèpre endémique*, but which, according to the description given by him, was certainly pellagra.

Theodori's observation regarding the presence of pellagra in Moldavia was based on an observation made in 1856, to which he added the experience of his father and other physicians of the country.[1] He considered it a new disease due to agricultural and economic changes which had brought about the substitution of imported maize for the wheat and other forms of food used formerly. In this work he showed that maize was first introduced into Europe in 1710 by the Prince Nicolas Maurocordato, antedating the introduction by Serban Cantacuzene, though the latter is usually given the credit for it. This latter introduction was not made until about the middle of the eighteenth century. He said that in his country there were no pathologic results for nearly a century. During this period no mention is made of the disease, either by the profession or by travelers. It was not until about 1830 that Boerensprung, following Theodori, wrote on this subject.

Sporadic cases of pellagra occurred in Vienna, according to Nicolas and Jambon,[2] as early as 1794. It is a notable fact that Billod first attracted attention to what he called pseudo-pellagra in the insane institutions and showed that it was the same disease

[1] De Theodori, Julius, "De pellagra — Dissertatio Inauguralis Medica."

[2] J. Nicolas and A. Jambon, "Contribution de la Pellagra et du Syndrome pellagreux." *Annales de Dermatologie et de Syphilographie*, 1908.

as true pellagra. He first found it in the insane institutions of Rennes and Sainte-Gemmes, and later he discovered it in the asylums of Dijon, Nantes, LeMans, Mariville, Quimper, and Par.

In recent years pellagra has been described in Mexico by Bouchard, and it has occurred in Brazil, Argentine Republic, Uruguay, and also in Africa. Sporadic cases have occurred in the Tyrol, Servia, Bulgaria, Greece, Asia Minor, and one case in England. Even more recently a sporadic case was discovered in the Shetland Islands.[1] Pellagra under the name psilosis pigmentosa was described about 1889 occurring in Barbadoes.

It has often been hinted by writers that the disease occurred among the American Indians prior to European invasion. This suspicion probably owes its origin to Strombio's statement that these people were very subject to sundry skin diseases. Probably the most authentic writer on the North American Indian was John Brickell, M.D., author of "The Natural History of North Carolina, with an Account of the Trades, Manners, and Customs of the Christian and Indian Inhabitants, etc." This work was published in Dublin in 1737. The writer was deputed by the government of the colony on several missions to the Cherokee tribe of Indians, and he has written a very full account of the diseases which he found among them at that time and which were known to the natives to have occurred in the past. It is probably in this work that we read the first reference in American medical literature to that all-absorbing topic of the present day among the physicians of the southern states, hook-worm disease. He described this condition under the term Cachexy and its symptoms were given as follows: "The Face is very pale and discolor'd, and the Body big and swoln, this Distemper is principally owing to their eating great quantities of Fruit that this Country produces, and to a sedentary way of living, and their eating Clay and Dirt which the Children, both White and Black, and some of the old People are very subject to, etc." This disease was declared very prevalent. The only cutaneous diseases mentioned are "Rashes and Prickley-heat, Tetter, and Ring Worms." He

[1] *London Practitioner*, 1909.

speaks, however, of yaws and describes it as a disease not well known in Europe, but very common here. He said it was like lues venera "having most of the symptoms that attend the Pox, such as Nocturnal Pains, Botches, foul Eruption, and Ulcers in several parts of the Body. . . . This distemper though of a venereal kind is seldom cured by Mercurials, as I have often experienced, for I have known some to undergo the Course of three salivations to no purpose, the virulency still continuing as bad as ever." His remedy was an infusion of the bark of the Spanish oak, the bark of the pine and sumac root. One might infer that a disease mistaken for syphilis which did not respond to mercurial treatment having the above-mentioned symptoms and for the relief of which astringents were used might be regarded as pellagra. The astringents would hardly have been in order for any other condition except diarrhea, which does not occur in syphilis, but which is seldom absent in pellagra. However, the assumption on this slim evidence of the real condition having been pellagra would not be justified. It seems reasonable to suppose that had pellagra existed in North Carolina then as it exists now, this very observant writer would not have overlooked it nor could he have escaped its detection, though at that time the disease had not been described nor the name coined. It is reasonable to suppose that the disease did not exist at that time in this particular colony at least.

It is altogether likely that the malady occurred sporadically in America for many years before its earliest detection. The most interesting fact in this regard was told me by Dr. Ch. Wardell Stiles. He says that he feels confident that the cause of the terrific death rate among the Federal troops imprisoned in the Confederate prison at Andersonville, Georgia, was hookworm disease and pellagra. Dr. W. J. W. Kerr of Corsica, Texas, is first hand authority for this opinion. The matter was carefully studied by Stiles, who thinks that it should vindicate the Confederacy from the charge which has been frequently made that the Federal troops were starved to death while the Confederates doing guard duty at this time were not affected, though it

has been shown that they received the same fare as did the prisoners.

In 1864 Dr. John Gray of Utica, New York, reported a case of pellagra. Doctor Tyler, of Somerville, Massachusetts, in discussing this case referred to a similar one of his own. Both these cases were in the insane. It is said that an epidemic of a disease strongly simulating pellagra occurred in an asylum for the insane in Nova Scotia. This outbreak was reported by J. deWolff. It is claimed that pellagra was diagnosed in the South Carolina Asylum for the Insane at Columbia in the early seventies by H. N. Sloan, but no report or record was made of it. Certainly the scourge existed among the inmates of this institution in the eighties, but it was attributed at that time to burns by sun or fire. D. S. Pope says that at least two cases occurred in the South Carolina penitentiary in the middle eighties.

In 1883 Sherwell of Brooklyn reported pellagra in an Italian sailor. In 1889 Bemis of New Orleans left a written diagnosis of a case in a white woman at the Charity Hospital in that city. In that year a case [1] occurred in North Carolina in the practice of the late Thos. R. Mask of Wilmington. It was diagnosed at the time as a form of psoriasis, but in 1907, when a large number of cases occurred in this same section, Doctor Mask described the case and I was convinced that the condition was none other than pellagra.

In 1893 Sandwith noted the occurrence of pellagra in Egypt and, becoming interested in the geographical distribution, he wrote to many physicians in the United States, but was unable to elicit any evidence of its presence at that time or the history of any past occurrence.

In 1902 Sherwell reported another case and H. F. Harris of Atlanta reported a case of anchylostomiasis presenting all of the typical symptoms of pellagra and which was an undoubted case.

Nineteen hundred and seven saw the first real scientific work on the subject in this country, and this year will stand out in

[1] Bellamy, R. H., and Wood, E. J., "Pellagra in North Carolina." Bulletin State Board of Health.

the medical history of this country as one of the most noteworthy, for then it was that this great scourge, which had been a known curse of Italy for over a century and a half, became a problem of vastest importance equaling in the southern states the problem of tuberculosis. Probably no medical subject has ever produced such profound interest on the part of the medical profession as did pellagra at that time and ever since. The man whose name will ever be connected as the discoverer of the existence of the disease in this country is George H. Searcy, who reported an epidemic occurring at the Mt. Vernon, Alabama, Insane Institution for Negroes. The cases were carefully studied by him, and also by E. L. McCafferty of the staff of this hospital. They were assisted by E. D. Bondurant of Montgomery and Isadore Dyer of New Orleans. This report embraced an account of eighty-eight cases with a fatality of fifty-seven. In this same year, 1907, J. T. Searcy reported nine cases from the Bryce Memorial Hospital in Alabama. Again, in this year, T. C. Merrill reported a sporadic case from Texas. The importance of Searcy's work can hardly be overestimated. Through the help of his report in the *Journal of the American Medical Association* within a few weeks the disease was recognized in half a dozen states and its identity with Italian pellagra irrefutably established. Our increasing knowledge of the disease brought about by a wider experience has added little to the description of Searcy. This observation was accurate and complete.

Before the appearance of Searcy's epoch-making report I presented to the American Medical Association in 1907 an account of a condition which I considered a symmetrical gangrene of the skin occurring in an insane man. To my mind the really remarkable condition in this case was a coincident infection with both tertian and quartan malarial parasites. This combination was practically unknown, no case having occurred of the kind in this country, though I was able to find a report of one case in Turkestan. The publication of this article brought forth many letters of inquiry from many quarters of the South, and by the help of these men, who had observed the same condition, the

diagnosis was determined. I was especially indebted to Searcy for his kind letter showing me my error and proving conclusively that the condition which I had ascribed to malaria was true pellagra and that the malaria was merely a coincidence.

In reading the "Proceedings of the Pan-American Medical Congress" for 1893 I recently found several diagrammatic cuts of a skin lesion and a number of water colors of a tongue condition, both of which were characteristic of pellagra. This article was entitled "Psilosis pigmentosa" and the author was Cuthbert Bower. To quote his opening paragraph: "During the past four years I have seen so many cases of chronic diarrhea — often ending fatally — in which a peculiar inflammation of the mucous membrane of the mouth is accompanied by a clearly defined pigmentation of the dorsal aspects of the hands and feet, that I have been forced to the conclusion that this triple association is not an accidental one, but is pathognomonic of an epithelial disease *sui generis,* possibly peculiar to Barbadoes, or else closely allied to a specific disease of the alimentary tract which has its habitat in the East Indies and has been accurately described by Thin of London as 'psilosis linguæ et intestinæ.'" He said that the Dutch physicians of Java recognized the condition as possessing characteristics sufficiently unique to distinguish it from the ordinary chronic diarrheas and dysenteries prevalent in tropical countries and gave it the name "sprue," a term also employed in certain parts of Scotland to designate aphthous stomatitis.

C. G. Manning,[1] medical superintendent of the asylum at Bridgetown, Barbadoes, reported in 1909 that for fifteen years there had occurred in the colony a disease generally called pellagra, but he rejected the diagnosis because it occurred only among the inmates of his institution and not among employees, though fed from the same kitchen. Hence the food, but more especially the maize, could not be accounted the cause, and he considered damaged maize the sole cause of the disease pellagra. His second objection was that the dark discoloration did not appear over the face, chest, and back, nor was it a true pigmentation in any

[1] Trans. Nat. Pellagra Cong., 1909.

sense. The third objection was that the eruption appeared and disappeared without leaving a mark. The interval of reappearance according to him was variable, but his most emphasized point was that it was not a true pigmentation. He claimed that he named the disease *psilosis pigmentosum,* and described it, claiming that it was not pellagra. His description is a very exact one of the condition which we understand to be pellagra in the southern states, differing in no essential detail, and is merely another one of the many good reasons for a hesitation in accepting the maize theory of the causation of pellagra.

As stated before, pellagra was found in Egypt by Sandwith in 1893.[1] Warnock stated that the disease was spread throughout Egypt by the use of bad maize and that only a portion of the *fellaheen* became insane. There were many cases in the asylum at Cairo, but this was not a fair estimate of the extent of the disease in the country. He further noted at this institution cases of insanity produced by pellagra.[1] From his annual report we glean the following information in the form of a table.

Year	Men	Women	Total
1896	9	2	11
1897	10	13	23
1898	10	29	39
1899	19	14	33
1900	8	27	35
1901	27	10	37
1902	23	10	33
1903	41	11	52
1904	38	15	53
1905	54	11	65
1906	46	13	59
1907	69	20	89
1908	71	17	88
1909	68	33	101
	493	225	718

[1] "Pellagra," by Marie, both in the original and also the translation by Lavinder and Babcock. Columbia, S. C., 1910.

This table shows the number of cases under observation. It is interesting to compare it with the table below which shows the number of deaths during a part of the same period. At the Kasr-et-Nil Hospital, Cairo, Marie [1] says there were in ten years more than one thousand cases. Many of these cases — about forty yearly — are committed to the asylum at Abbassia on account of a resultant insanity. Sandwith thought that about 36 per cent of the Egyptian peasantry were affected. The proportion in better conditioned neighborhoods falls to 15 per cent, but elsewhere rises to as much as 62 per cent. In upper Egypt the dryness of the atmosphere and the use of millet in place of maize, according to Marie, has made the danger much less.

Deaths from Pellagra at the Cairo Asylum

Year	Men	Women	Total
1901	6	4	10
1902	6	2	8
1903	9	1	10
1904	3	3	6
1905	13	4	17
1906	9	1	10
1907	7	2	9
1908	6	2	8
1909	10	5	15
	69	24	93

R. H. Bellamy of Wilmington and J. B. Wright of Lincolnton were the first physicians in North Carolina to recognize pellagra. Bellamy made his first diagnosis prior to the appearance of Searcy's article, but his report was not read until 1908 before the American Medical Association.[2] To him I am indebted for the first sight of the disease. His first cases, five in number, were studied in 1905, though we did not identify the condition with pellagra, as we had always been taught that this disease did not occur in this country. Long before we learned the cor-

[1] Marie, A., "La Pellagra," Trans. by Lavinder and Babcock.
[2] Bellamy, R. H., "Pellagra." *Jour. Am. Med. Assoc.*, 1908.

rect name we were entirely familiar with the disease picture and especially with the prognosis, for at that time there were no recoveries except exceptionally, as the disease assumed the acute form, about which there will be a later mention.

In 1908 J. J. Watson and J. W. Babcock of Columbia, South Carolina, went to Italy and investigated pellagra in order to prove or disprove the identity of the disease in the United States with that of Italy. They were thoroughly convinced that there were no points of difference. Prior to this Babcock [1] had written a report in the form of a query regarding the outbreak of pellagra in the South Carolina Institution for the Insane at Columbia. In this paper the suggestion was made that pellagra did exist in the institution. This article was published in several different places and attracted world-wide attention. Much credit is due Babcock for his enthusiastic work in bringing this disease before the attention of the American medical profession, to whom it was entirely unknown, even theoretically. To his activities are due the various movements which resulted in the establishment of the National Pellagra Conference, which meets yearly, and already through its two meetings has done much to promulgate a better acquaintance with this great scourge.

In 1908 C. H. Lavinder of the United States Public Health and Marine Hospital Service stationed at Wilmington, North Carolina, had his attention for the first time directed to the disease. Through the courtesy of the local physicians he was given an opportunity to see a number of cases. At that time these men were thoroughly acquainted with pellagra, having had it in their midst since 1905, and they had collected valuable data not only from abundant clinical material, but also from the foreign literature. At that time there was no literature on this subject in English, but they had for their own use made a few translations, chief among which was the work of Tuczek. On reporting the existence of this disease to the late Surgeon-General Wyman Doctor Lavinder was at once ordered to prepare a précis for im-

[1] Babcock, J. W., Report, S. C. Board of Health, 1907, and *Am. Jour. of Insanity*, 1907.

mediate publication. This paper was largely the gleanings from the work of Procopiu in French and the above-mentioned work in German. In the meanwhile one patient with the disease was admitted to the Marine Hospital at Wilmington. This précis was very generally distributed and constituted one of the first authentic publications in this country. Through it the matter was brought officially to the attention to the profession, the public, and most important of all, to the United States Public Health and Marine Hospital Service, which since that time has done a great deal of valuable work on the subject and proven to many the great importance of this great strong arm of the national government.

In 1908 the South Carolina Board of Health held a conference on pellagra, and in November, 1909, a national conference was held in Columbia under the same auspices.

In 1909 it was estimated that at least one thousand cases of pellagra occurred in sixteen states, and it was conservatively estimated that fifteen hundred cases had occurred in the southern states since 1906. In 1910 the malady was suspected or shown actually to occur in thirty-three states, and the number of cases approximated three thousand and a total of five thousand had occurred in five years. Foci of the disease were discovered in insane institutions of Alabama, South Carolina, Georgia, North Carolina, Florida, Louisiana, and Virginia.

The pathologic study of the nervous system in pellagra made by H. A. Cotton, superintendent of the New Jersey Hospital for the Insane, has opened up a most interesting field of speculation and study. The findings thus far have led him to think that it is not improbable that the disease has occurred in northern institutions unrecognized for many years. In a personal communication from H. A. Hurd of the Buffalo Hospital for the Insane I was impressed with the possibility that there was pellagra in his institution under the diagnosis of general paralysis of the insane. In 1906 I showed my photographs of pellagra to Doctor Hurd and he suggested this explanation of the matter. At that time I did not know that the condition was pellagra and I

do not now know what Doctor Hurd's present views are. He informed me that such a skin lesion as shown in my photographs was not uncommon in his paretic cases. I met this same experience in the North Carolina State Hospital for the Insane. A patient of mine was sent home from that institution on leave. I was curious to know the reason for her wearing cotton gloves, and on inquiring was told that her hands were sore. An examination showed not only the typical symmetrical erythema, but also the characteristic tongue and diarrhea confirming the diagnosis of pellagra. Through the courtesy of James McKee, superintendent of the institution, as well as his carefully kept clinical records, the fact was demonstrated that pellagra had existed in the hospital for a number of years and had been counted merely an occurrence with dementia paralytica. In this same connection it is interesting to note the occurrence in the Cook County, Dunning, Bartonville, and Peoria, hospitals for the insane. Since that time much important work has been done in Illinois. In June, 1910, J. D. Long of the United States Public Health and Marine Hospital Service verified the diagnosis in nine cases in the Philadelphia General Hospital (Blockley).

Special commissions for the study of pellagra have been appointed by the United States Public Health and Marine Hospital Service, by the governor of Illinois, by the North Carolina Board of Health, by the Tennessee Board of Health, and by the New York Postgraduate Medical School. This latter institution is about to establish a field laboratory for the more intimate study of the disease. At this writing L. M. Sambon of the London School of Tropical Medicine with a number of interested workers is in the Austrian Tyrol under a Wellcome grant experimenting with the Simulium reptans as the intermediate host in the transmission of the disease. This hypothesis which will be again referred to was promulgated by Sambon in 1905 before the British Medical Association and since that time has grown rapidly in favor.

Throughout the South pellagra is the live topic of medical interest, and rightly so, for it has become as great a problem as

it has been in Italy since Strombio reported it in 1784. The disease is either on the increase or else is being more generally recognized, and already two special institutions for its treatment have been established. In North Carolina, at least, it is second only to tuberculosis in importance. One town of twenty-five thousand in this state has already reported two hundred cases. In 1909 I made a statement before the North Carolina Nurses Association that there were in that state one thousand cases. This statement was made the object of ridicule by the press of the state, who refused to accept this unpleasant fact. Only a few months later the Board of Health estimated the number at three thousand. It is thought by many that at this time the number would be much nearer ten thousand.

In Roumania in 1901 there were 33,645 cases; in 1905, 54,689 cases; in 1906, more than 100,000 cases. It is stated by Marie, from whom these figures are taken, that only three cases occurred in Bucharest, and that the disease is largely confined to country districts, accounting, according to this author, for the high infantile mortality. It is further stated that the staple food of the peasantry is maize and the 1909 crop was 126,000,000 bushels. Of course, the cause of the disease is ascribed to the use of this form of food.

In 1882 Marie said that Henry Strachan, senior medical officer, reported 510 cases of what he called malarial multiple peripheral neuritis, which he observed in the Kingston, Jamaica, Public Hospital. The patients complained of numbness and burning heat in the palms and soles, often accompanied by cramps which were worse at night and in bad weather. Impaired hearing and vision with a feeling of constriction around the chest were reported. There was an eczema of the eyelids, the angles of the mouth, and the mucocutaneous margins of the nostrils. Pain in the hands and feet was noted. There was notable emaciation. Pigmentation of the palms, soles, and lips occurred. When death occurred it was due to respiratory paralysis, but this was exceptional, as the disease was comparatively trivial. The subjective symptoms are summarized thus: dimness of vision, im-

paired hearing, numbness and cramps of the extremities, girdle pains, and joint pains. The objective symptoms are: trophic changes, monoplegias, altered gait, the knee jerk absent in over one-half, exaggerated or subnormal in 23 per cent, and normal in the remaining cases, cutaneous reflexes varied greatly, sensation blunted or absent, soreness of the mucocutaneous lines of junction, and wasting of the muscles. Soreness of the mucocutaneous borders of the eyelids, lips, urethra, anus, or vulva were among the first symptoms. Wasting and contraction of the muscles occurred in extreme cases and the result was the "claw" hand or foot. There was some retinal hyperaemia, seldom enough to be counted as optic neuritis, but there was pigmentation of the fundus. Pigmentation of the brain and the spinal cord were the only changes noted post mortem. Strachan thought the condition was due to malaria, but this view has not been generally accepted.

Braddon in speaking of food poisons said: "Another disease probably owning similar etiology is Strachan's disease occurring among the natives of the West Indies, which in some respects resembles pellagra. The West Indians live largely, too, on maize."

Sandwith in a private letter referred to in Lavinder and Babcock's translation of Marie's work, which has been freely drawn on for this data, says that Strachan did not describe either beri-beri, multiple neuritis, or pellagra, but that it is possible that the condition is post-dysenteric neuritis, of which there is a great deal in the West Indies. The nervous symptoms are very different from those of pellagra, in which condition there is not the uniformity of symptoms as Strachan described. It would be equally as well in order to consider acrodynia as pellagra in this connection. Sir Patrick Manson says it differs from beri-beri in the absence of edema, and he does not think that it can be ascribed to malaria, but is more likely a specific disease entity in itself. It is interesting to note the confusion regarding the classification of this condition, and one is made to think that if such doubts can arise at this time of great medical advancement it is not to

be wondered that the early observers often experienced difficulty in their classifications.

Wollenburg of the United States Public Health and Marine Hospital Service, reporting to his department from Naples, says:

"Pellagra, despite the extensive interest which is being taken in its suppression, continues to spread in certain regions of Italy. A vigorous campaign has been waged against the disease for a number of years, laws concerning it have been enacted, improvements in grain culture have been encouraged, sanitation has been widely improved; the number of pellagrins, however, is diminishing but slowly. The sum total which is annually expended for salt, proper food, and hospital accommodations for the care and treatment of the poor affected with pellagra is enormous. During the past twenty-five years the extent of the disease has lessened considerably in the northern part of Italy — Piedmont, Lombardy, Venetia, and Emilia — while there has been a persistent spread in central Italy, very notably in Tuscany, Marches, and Umbria. The disease is now appearing in alarming proportions in Latium and in Abruzzo and Molise, compartments in which it was unknown some years ago. What is more striking is that the disease invaded southern Italy in 1908, cases having occurred in the vicinity of Naples and in Calabria. At present pellagra appears to be firmly established in the lower as well as in the upper portion of the Italian peninsula. The reason for this better showing in the north is not altogether plain, but it is partly attributed to the economic, social, and sanitary improvements that have been effected there in recent years. In the last triennium the disease was markedly reduced in the provinces of Arezzo, Bologna, Brescia, Florence, Forli, Macerata, Mantua, Modena, Padua, Pavia, Perugia, Pesaro, Rovigo, Treviso, and Venetia. An increase took place in Bergamo, Milan, and Novara. Statistics for central Italy show marked improvement in the province of Perugia. For the rest, the status remains nearly unchanged. In southern Italy there are new cases in the provinces of Avellino and

Cosenza. In the same period the total number of new cases reported for the whole country has been gradually reduced as follows:

	New Cases		New Cases
1906	6783	1908	2766
1907	5307		

"The total number of pellagrins in Italy at the present time may be estimated at less than 50,000. Considering that during the years 1906 and 1907 pellagra was the cause of 1873 deaths and 1293 cases of insanity, together with the long duration of the illness and its effect on the earning capacity of the afflicted individuals, the above figures are sufficiently startling.

Total Number of Pellagrins by Census

1879	97,855	1899	72,603
1881	104,067	1905	55,029

"The mortality seems to be lessening. It changed very little after the law of 1902 came into effect until the years 1906 and 1907, when there was a fall in the number of total deaths to less than one-fifth of those during the preceding years.

Total Deaths from Pellagra in Italy

1898	3987	1903	2647
1899	3836	1904	2363
1900	3788	1905	2357
1901	3054	1906	437
1902	2376	1907	376

"The hoped-for results and salutary intent of the law — to prevent the consumption of maize of poor quality — have hardly been realized. The law permits the milling of low grade maize in case it is not to be used as an aliment for man, but this provision is held to be hard to enforce, proper sanitary supervision being very difficult."

Number of Pellagrins in Compartments by Census [1]

	1881	1889	1905
Piedmont	1,328	1,223	1,012
Liguria	56	30	56
Lombardy	36,630	19,557	15,746
Venetia	55,881	39,882	27,781
Emilia	7,891	4,617	3,357
Tuscany	924	1,125	1,137
Marches	406	920	1,436
Umbria	872	5,103	4,250
Latium	32	146	195
Abruzzo and Molise			59

A correspondent of the American Medical Association [2] from Vienna wrote the following interesting letter, which was reproduced by Lavinder and Babcock:

"In the eastern part of the Empire a disease has been very prevalent among the poorer classes for some years past which has proved puzzling to the profession. The clinical symptoms somewhat resembled those of lepra, but differed in not having the anesthetic patches, with consequent dystrophic destructive processes. Profound cachexia with gastrointestinal disturbances are generally observed after the disease has persisted for from twelve to eighteen months. In many instances these were the only symptoms, while in other cases circulatory disturbances are a prominent feature. Similar cases were reported from neighboring districts of Russia and Roumania, and many scientists studied the disease. It was finally agreed by the majority of the investigators that the cause of the condition lay in the food. The peasants live largely on maize, making bread and other foods out of this material; a dish called 'polenta,' consisting of coarsely ground maize with lard, is partaken of heartily daily. In certain wet years the corn was affected by a sporidium and became still more unwholesome because of the presence of

[1] Lavinder and Babcock's Trans. of Marie's "La Pellagra."

[2] *Journal Am. Med. Assoc.*, Aug. 1, 1908. Lavinder and Babcock's translation of Marie's work, p. 61.

certain toxic substances which are held responsible for the disease just described — pellagra. In the province mentioned, inhabited by 1,500,000 people, there are over 38,000 cases reported (3 per cent)." [1]

The above-mentioned correspondent a little later again wrote:

"Since 1905 the action of the government in suppressing pellagra has been going on and including all affected areas. Altogether a population of 2,250,000 has been investigated with the result that about 78,163 persons (3 per cent) were found to be suffering from one form or another of the disease. Certain districts were more affected than others, and, as a rule, the poorer classes succumbed more easily than those who could procure the food regarded as necessary. The measures of the government have been of a prophylactic nature."

Lavinder and Babcock give the following interesting account of pellagra in Transylvania:

"An account of pellagra in Transylvania is given in the *Lancet* of July 16, 1898, p. 164. Transylvania is in the Carpathian Mountains, on one side being inhabited by Hungarians, on the other by Roumanians — the descendants of Roman legionaries of the time of Trajan and his successors.

"When an endemic outbreak was reported from Transylvania a commission was appointed and confirmed the diagnosis of pellagra. But fifteen years previously Doctor Takach reported suspicious cases of skin diseases which he named pellagra, but this diagnosis was questioned by a dermatologist of Budapest. In 1897, however, special orders were issued to hospitals and asylums to be on the lookout for pellagra. Doctor Takach was the first to send in a patient suffering from pellagra. After that numerous cases were found. The disease was thought to be the result of insufficient nourishment, aggravated by bad hygienic conditions and

[1] *Jour. Am. Med. Assoc.*, Sept. 4, 1909. See also Lavinder and Babcock's translation of Marie.

malaria. No cases could be detected where the people had good and sufficient food. The disease seemed to follow continuous rains, bad crops, and murrain among the flocks."

In 1910, in a consular report, Vice-Consul W. Bayard Cutting, Jr., at Milan said that in 1770 pellagra was almost unknown in Italy, but that in 1839 in Lombardy alone there were over 20,000 and in 1879 over 40,000 cases. In 1881 the provinces of Piedmont, Lombardy, Liguria, Venetia, Emilia, Marches, Umbria, Tuscany, and Lazio having all told a population of 16,689,735 contained 104,067 victims of the disease. These figures cannot represent all cases because of defective reports, and yet even this represents one case to every sixty of the rural population, while in such regions as Venetia away from the agricultural district the proportion was only one to nineteen. He claimed that the spread of the disease was confined to those regions where maize formed the chief food. Maize, according to this observer, was introduced into Italy from the Balkan States.

In this same report [1] Babcock has collected some very important data regarding the distribution of the disease. While it will be noted from his table that the disease is much more prevalent in the southern states the fact can not be lost sight of that the disease is generally distributed and deserves more of the attention of the profession generally than has hitherto been accorded to it. From what has been said on a previous page it will be recalled that there is some ground to suspect that an atypical form of the disease has been occurring for some years in the northern institutions for the insane and that this matter deserves more attention and study than it has received.

[1] "Prevalence of Pellagra," by J. W. Babcock and W. Bayard Cutting. Public Document No. 706.

Prevalence in the United States[1]

Massachusetts	3	Tennessee	51
New York	3	Kentucky	5
New Jersey (imported)	1	Illinois	250
Pennsylvania	33	Iowa	2
Maryland	7	Kansas	2
Virginia	100–300	California	7
North Carolina	200	Indiana	1 (?)
South Carolina	500	Ohio	1
Georgia	670	Colorado	1 (?)
Florida	50	New Mexico	2
Alabama	330	Missouri	3
Mississippi	188	Vermont	1
Louisiana	500 (?)	Rhode Island	1
Texas	100	West Virginia	1
Oklahoma	1	District of Columbia	1
Arkansas	1		

Note. — Later reports of cases of pellagra have been made from Wisconsin, Washington, Michigan, and Oregon. Under date of October 3, 1911, a report was made to the Tennessee Board of Health by the commission appointed to study the disease in that state. This was probably the most complete work of the sort yet done in this country and is a great credit to that state. The report was based on an observation of three hundred and sixteen cases, though the committee estimate the number of cases in the state at twenty-five hundred. To quote the report in this place would not be in order, as it will be referred to at length later, but the tables are of much importance and a number are here given.[2]

Number of counties in the State	96
Number of counties visited	64
Number of counties found with pellagra	58
Number of counties with pellagra not visited	9
Total number of counties with pellagra	67
Number of detailed reports on file	316

[1] Babcock, J. W., "Prevalence of Pellagra." Consular Report No. 706, Washington, 1911.

[2] "Pellagra: Report upon 316 Cases of this Disease as submitted by the Commission Appointed by the Tennessee State Board of Health."

Total Cases	316		
Male Whites	98	Male Colored	4
Female Whites	200	Female Colored	14

With each day comes news of further extension of the scourge and it seems that the conditions in the United States are as favorable as in Italy, where the disease has done so much to retard the progress of that country. The question is one that should engage the attention not only of the medical profession, but of the public generally.

It is possible from what has gone before that the reader will agree with me that pellagra was probably an ancient disease; that the proofs of its antiquity are fully as well established as those of its modernity. Sambon especially, among recent writers, is very positive from historical proofs that the disease was known many years — even centuries — before the introduction of maize into Europe. He brings out proof after proof that the older writers considered it a form of scurvy and shows that even the great authority, Marzari, whose writings have been of so much importance, proposed the name of "Italic scurvy." In his treatise on scurvy Della Bona probably alluded to pellagra when he said: "Interdum, sed rarius apud nos cutis finditur, asperi tudinemque habet, et squamas quasdam remittit sic ut ad eum morbum accedat quam graeci elephantiasim vocant."

Regarding the probability of the overlooking of pellagra in earlier times Sambon wrote:[1]

"The previous non-recognition of this disorder is by no means surprising. The history of many other diseases in this respect is similar to that of pellagra. It would be idle to seek for descriptions of typhoid fever among the medical writings of antiquity or of the Middle Ages, and yet this disease was no new malady when definitely extricated in the eighteenth century from the old 'fevres pestilentes.' The history of rickets is just as obscure prior to Whistler's thesis (1645) and Glisson's famous treatise;

[1] Sambon, L. W., Progress Report on the Investigation of Pellagra. Reprint from *The Journal of Tropical Medicine and Hygiene*, 1910.

yet it would be a great mistake to believe that the so-called 'morbus puerorum Anglorum' appeared as a new disease at the beginning of the seventeenth century and broke out for the first time in the English counties of Dorset and Somerset. Scarlet fever was not recognized as a distinct disease before the seventeenth century, when the works of Sennert, Doering, and Sydenham crystallized the medical comprehension of this morbid process. It would be absurd to believe in any of the dates assigned to the first appearance of this disease in the various European States. In all probability it had long existed, but had always been confounded with measles. Scurvy is another disease, the history of which does not go further back than the fifteenth century, when it was brought prominently to notice by the havoc it played aboard ship, as in Vasco de Gama's great voyage round the Cape in the year 1497, when 100 out of a total of 160 men succumbed to it. Until a few years ago kala-azar was looked upon as a disease peculiar to Assam. The discovery of its causative agent by Sir William Leishman, in 1903, made the diagnosis comparatively easy, and the disease was soon reported from Ceylon, China, North Africa, Sicily, and other parts. Its late recognition in these places, however, does not in any way signify recent importation.

"Returning to pellagra, it is interesting to notice that the disease was recognized in Egypt by Pruner as early as 1847; but Pruner's statements were discredited by Hirsch, and almost half a century elapsed before it was definitely proved, by Dr. Sandwith's investigations, that pellagra is one of the scourges of Egypt, and a very serious one among the *fellaheen* of the lower country. The case of the United States of America is again most instructive. Until quite recently all American text-books stated quite emphatically that pellagra was unknown in that part of the world; then suddenly the disease is discovered in no fewer than twenty-six states. This wide distribution of the disease, the diagnosis of a few cases as early as 1863 or 1864 in the New York and Massachusetts asylums, and the absence of any definite history of recent importation or outbreak show very clearly

that the disease is of long duration in the United States, yet it escaped recognition.

"A fact which powerfully suggests that pellagra could not have appeared for the first time in Italy about the middle of the eighteenth century, but that it must have been very ancient, is the wide distribution it had already attained at that time. Indeed, we know that it ranged throughout the north of Italy from the Julian Alps to the Alps of Piedmont, from Lago Maggiore to the Arno. I have already mentioned that Pujati saw the disease at Feltre about 1740, and that Nascimbeni a few years later recognized it in Friuli. Soler (1791) found it along the River Piave in the district of S. Polo, Sartogo (mentioned by Franzago, 1791) in the neighborhood of Aviano, Aldalli (mentioned by Soler, 1791) near Sarone, a village at the foot of the Julian Alps. Fanzago (1804) states that Doctor Storni, who practised for over forty years in Campo S. Piero, Padua, had never observed any difference either in the number of persons attacked or in the severity of the disease. He believed that the malady could not be looked upon as of recent origin, since his predecessor, Doctor Carlo Barbanti, who had taken up residence in that district thirty years before him, about 1730, had stated that he had always observed it in those places. A work published in Naples in 1788 under the title "De epidemicis et contagiosi morbis" mentions the existence of pellagra in the territory of Modena. Tarzaglii (1794) states that the disease had been noticed previous to 1730 in the vicinity of Sesto Calende (on Lago Maggiore); Albera (1781) says: 'Doctor Brava, a man of repute and learning, has told me that pellagra had been known for over sixty years (1720) in the Ligurian mountains; it proceeded in the same order, and manifested itself and grew with the same symptoms. . . .'

"A sudden influx of literature on a newly described disease is not necessarily an indication of recent appearance or unusual prevalence. Speaking of typhoid fever, Hirsch says: 'This large amount of writing on typhoid, especially between 1830 and 1840, has given rise to the often expressed opinion, which at one time I shared, that we have to do with unusually general prevalence

of the disease during that period, or that its general diffusion had not been reached until recent times. I think, however, that we must consider this to be an erroneous view, and that we must explain the phenomenal outburst of literature by the sudden and rapidly culminating interest of the profession in a new and important object of study — a phenomenon which has recurred in the case of many other forms of disease.'

" The sudden flood of American literature on pellagra and the recognition of the disease throughout the greater part of the United States since 1908, when Doctor J. W. Babcock inculcated its grave importance, are but a repetition of what happened in Italy at the close of the eighteenth century."

CHAPTER II

THEORIES OF ETIOLOGY

The cause of pellagra is unknown, and, indeed, at the present time there is more uncertainty about the whole matter than ever before. For nearly two centuries and, in fact, since the time of the first known writer on the subject, Casal, maize or Indian corn has been the supposed cause. In the minds of most pellagrologers it would be as absurd to expect ergotism in one who had never eaten spurred rye as to expect pellagra to be due to any other cause than altered maize. But in the case of ergotism and spurred rye there is no contention, as it is an accepted fact by all observers without exception that there is one and only one cause, and there has been no contradictory evidence. The case of pellagra and damaged maize is different. Since the very first of our knowledge of pellagra there have been enthusiastic advocates of the maize theory, but there have also been those equally opposed to it. It is likely that the matter would have rested in this unsettled state, had it not been for the fact that such observers as Billod attempted to separate true pellagra, a disease in which the patient did eat maize, from false pellagra in which the patient did not eat it. The clinical description of false pellagra is absolutely the same as for the true and one cannot but feel that such a view is merely begging the question. It is my intention in this chapter to give the various theories without prejudice, but it is also my intention to show the lack of scientific accuracy which from the start has so largely characterized the study of the question.

We are told that Casal in his description of *Mal de la Rosa* mentioned maize as one of the probable causes of the disease.

The elder Strombio was very positive in his opinion of the resemblance of pellagra and scorbutus. He said that the country

people who were subject to the disease inhabited miserable damp rooms, and after the work of summer was done spent the time in great laziness without regard to cleanliness. He thought that such a manner of living was also responsible for scurvy, though he recognized the fact that the two diseases were very distinct. He thought that moist air and dampness had a great influence on scurvy but emphasized the point that pellagra occurred in high, dry countries.

Throughout the history of the scourge all writers have agreed on the one point, that workers in the earth living in rural districts are almost exclusively the class of people affected. Recently this fact has been made use of to aid in proving the correctness of Sambon's hypothesis — that the disease is transmitted by a fly which is a field pest. It is notable that Albera and Odoardi found it in people leading a quiet, inactive life. My own experience does not altogether bear out the contention of Strombio, for I have found the disease well defined in merchants, professional men, women of the higher walks of life, and in people who lived well but did no work of any kind.

The action of the rays of the sun was thought by Frapolli to be the sole cause and Gherardini, who had the same view, said that he produced opisthotonus in pellagra by allowing the victims to be exposed to it. But Frapolli thought he was dealing with a skin disease and in this he was mistaken. He thought that the internal manifestations were the result of the skin lesion and the severity of these symptoms depended on the severity of these local manifestations. At the present time the actinic rays of the sun are thought by some to be an exciting cause in the production of the erythema.

Zanetti thought that bad food was a definite cause and also that the condition was favored by bad air and poor hygiene. Gherardini, who seemed to have the happy faculty of often changing his views, is accredited with the opinion that it might be caused by the consumption of Turkish wheat (maize) or other damaged grains as well as by poorly cooked breads and the abstinence from wine among those accustomed to it. Albera opposed the view that bad bread or abstinence from wine was a cause, and advocated the

idea that the trouble was due to change of climate, neglect of the body, and the eating of flour, chestnuts, lentils, and poor quality of plant food. Odoardi thought that the lack of salt in the polenta was a cause. It should be remembered in this connection that salt was a government monopoly and often beyond the reach of the poor peasant. The mixture of rye and maize was named as a cause, as well as soft cheese made of goat's and cow's milk. Strombio said that, while the idea of bad food being the cause of the disease was generally accepted in his time, each observer had a special opinion of his own as to the exact character of this deficiency. As we follow the disease down through the years and finally see maize the only food stuff incriminated we find a repetition of this diversity of opinion though practically all were willing to unite on the general proposition. It is really interesting to enumerate the various views of the supposed noxiousness of maize.

Strombio suggested the idea that possibly the seed of some noxious weed had become mixed with the grain. One of the old observers wrote thus: "The weather was bad and there grew much weeds among the wheat and many people had headache, and in summer ulcers, showing a bad condition of the fluids. I found several cases of pellagra among these people."

Strombio, who wrote in 1784, stated that his predecessors supposed the cause lay in scanty and insufficient nourishment as a general cause, but he thought that this could not be a specific cause and mentioned a number of examples. He said that while some authors thought dry air, sudden changes of weather, and the hurtful action of certain plants were responsible, he found only that it was at home in poverty and bad hygienic conditions. He said: "I look into my case book and find that bad hygiene is the chief cause. People entirely healthy who develop intermittent fever also develop pellagra. Rachitic children and chlorotic girls were peculiarly susceptible. . . . Several women previously healthy would develop the disease in pregnancy or during the puerperium. Pellagra has an infinite number of causes. Bad food is an important but not a sole cause and, finally no cause alone is likely to bring it forth."

Boerhaave described the disease and considered it due to certain disturbances of excretion. Odoardi, following out this theory, decided that it was due to the effect of certain abnormal acids in the system.

Strombio considered the seat of pellagra to be in the stomach and thought he could prove his claim at autopsy. He said that this would easily explain the relation of the abdomen, the head, and the skin. Like Ramazini he thought that an accumulation of mucus in the stomach or lower bowel would explain the disease.

Albera tried to find the cause by actual experimentation. To test the action of a strict vegetable diet he chose different groups of patients. All groups receiving bread and wine were relieved of the trouble for the time, though Albera concluded that it merely retarded the progress of the disease which would continue to recur in each successive spring.

Vincenzo Sette thought that moisture caused a digestive disturbance resulting in pellagra. He did not think that the cause could be found in the climate. He said: "I have traveled through all sorts of country and have seen the habitations of both rich and poor, but regardless of this it is more prevalent in sandy regions. It also occurs in high countries where there is water and also where there is no water. An improvement of general hygiene causes a disappearance of the disease."

Albera, Soler, and Sartago found a cause in poor ventilation.

In 1832 Spesa [1] found a more definite and scientific cause in the "exhalation of ammoniac which comes from internal fermentation in the midst of which pellagrins live." Facheris and Gherardini always considered this theory unreliable.

All the earlier writers tried to connect the appearance of the disease in country people with the etiology. It was thought that the exposure to the changing weather or the hard labor with a lack of sufficient nourishment might be contributory. Facheris wrote: "In these more recent years it is hard to see why the larger number of beggars, the artisans of both sexes but especially the weavers,

[1] Spesa, Anna Univ. di Medic., 1832, no. d'Oct. et Nov. Quoted by Roussel.

and others not exposed to the action of the sun or making their living by the earth, have pellagra."

Toward the middle of the nineteenth century all writers adopted the idea that pellagra was a disease of malnutrition though it might affect the rich as well as the poor.

Del Campo traveling in Pola de Siero saw *Mal de la Rosa* suddenly appear among a people who ate much maize and grew it as well under a burning sun. He thought the appearance was the result of the accumulation of heat in the blood. Fifteen years before this, Vay, while studying electricity, concluded that pellagra was the result of the abnormal accumulation of electric fluid in the blood.

There were several to advocate a miasmatic theory of the causation of pellagra. Chief among these was Thouvenel. He believed that the numerous irrigation canals and the rivers of the Lombardy plains considerably increased the evaporization. He thought that the air of the near-by Alps was dry and bracing but that at the foot hills of these mountains where these two different atmospheres met there was produced a condition which favored the development of the malady and thereby he accounted for the prevalence of the disease in what has been often referred to in the preceding chapter as the sub-Alpine country. There were many objections to this view.

Ten years after Frapolli Albera resuscitated the theory of insolation but he met opponents both in Facheris and Strombio. Rousel said that he referred to the disease as *maladie de l'insolation du printemps*. Facheris thought that if the disease depended on the sun's rays it would be more apt to appear when the rays were hottest and not early in the spring before warm weather. Strombio insisted that there must be some internal morbid cause which rendered the skin more susceptible to the action of the sun. He said further that if pellagrins avoid the sun they escape at least a portion of the skin disturbance, but this does not retard the progress of the disease. This view expressed nearly a century and a half ago is as accurate according to present-day belief as any that has so far been brought forward. I have compared the rôle of the sun

in the production of the erythema to the photographer's sensitive plate which is ready to receive a light impression but which will forever remain a blank without this action of the light. And on the other hand I have repeatedly seen an erythema appear on the feet of patients in the hospital confined absolutely to bed. It will later be brought out that this erythema of the covered portion of the body differs from that of the exposed portions in that the well defined lines of demarcation between diseased and normal skin are lacking. It should be emphasized at this point that the extent of the skin lesion is in no sense an index of the severity of the attack. I have seen the so-called pellagra universalis or pellagra with a skin manifestation covering all or nearly all the skin surface when the attack was most trivial and the patient able to remain at work. On the other hand I have seen cases of fatal pellagra in those with so trivial a skin disturbance that it would actually be overlooked by the patient himself. Then, too, if the sun has even a favoring influence in determining the position of the skin lesions why is the perianal skin and the vulva as well as the skin of the bend of the knee so often the locations? Again it would be obviously unfair to overlook the fact that the exposed parts are affected about one hundred times to one time of the unexposed. I have seen the skin lesion generally distributed over the upper thoracic and back regions in a young woman, but it was noteworthy that the portions of skin surface beneath the shoulder straps of the chemise were definitely outlined by being absolutely unaffected by the erythema. Experimenters have been able to produce areas of erythema at will by making holes of the desired size and location in the clothing of a pellagra patient.

In 1862 Bouchard expressed the opinion that the influence of the sun was purely secondary and that the real underlying cause was poor nourishment. Landouzy wished to know if the sun was suppressed what would become of pellagra. Roussel answered that to suppress the sun would not suppress pellagra. The sun he thought did not cause it but was an enemy to pellagra. In 1843 Marchand thought it of sufficient moment to write that he found the disease under the sign of the zodiac, Belier.

Roussel thought that there were enough evidences to prove that the name *mal de misère* was a misnomer. This name owed its origin to the occurrence of pellagra among the wretched peasantry of Italy. Roussel contended that this could not be the sole cause because the disease was not confined to this class. This fact has been even better demonstrated in the United States than it was in France in the time of Roussel's writing. I have had many patients suffering with typical pellagra among the best conditioned classes, but, of course, this would not answer the argument entirely because a patient may suffer from malnutrition in the midst of plenty. I might add that I have observed the disease in the well nourished as often as in the poorly nourished. The idea of the disease being one of malnutrition is due to the fact that the patient usually does not consult the physician until the disease is well advanced, or, on the other hand, the physician does not at once diagnose the condition. There are many good reasons for a delay in the diagnosis of pellagra. One of the most important is that the skin lesion remains only a comparatively short time and may be so slight as to attract almost no attention even from the patient. It is never good policy to make a diagnosis of pellagra without the presence of the skin disturbances unless the history of the skin lesion is very definite. It will be later shown that sprue occurs in the southern states and pellagra without the skin symptoms cannot be differentiated from this disease. From this the reader will see that pellagra is well advanced oftentimes before the diagnosis is reached, and by that time there is every reason to expect a condition of malnutrition as much as one would expect the same thing in dysentery. All diarrheal diseases are attended with rapid wasting and pellagra is not an exception. In my own experience I find that pellagra causes malnutrition but is not caused by it any more than furnishing a simple predisposition and this is no more emphasized than in typhoid or any other like process. Roussel said that the cause was not bad air nor bad water but bad nourishment. It cannot yet be denied that bad nourishment in the sense of containing something toxic is the cause, but I can deny that bad nourishment in the sense of insufficient nourishment is a cause.

Jacobo Penada thought that the cause was to be found in the absence of wine from the dietary. There was abundant contradiction to this and later it was proven that alcohol was a decidedly active predisposing cause. I have had ample occasion to suspect that alcohol did play a very definite part in the causation of the disease, and were it not for the fact that pellagra is so apparently due to a very definite specific cause I would undertake to show that the effect of alcohol was very decided. This last mentioned observer also thought that a cause was to be found in the use of salty food. Salt in the pellagrous districts of Italy was a luxury because it was, as before mentioned, a government monopoly and the price placed it beyond the reach of the poor. Roussel and later Lombroso emphasized the importance of salt in the dietary as a prophylactic, and the latter went so far as to say that salt would do as much in the treatment of pellagra as arsenic were it not for the fact that it was not well borne by the stomach.

The cause was also sought in bad rye bread, in the use of lard pastry, in millet, and even in rice. Zanetti answered all these theories by declaring that the real cause was the nourishment, which consisted chiefly of maize in Lombardy, where he did his work.

In 1778 Thouvenel brought forth the view that the cause of the disease in the valley of the Po was a condition of the atmosphere, but the French physicians thought that this condition merely affected the maize which was the chief article of diet. It was attempted to prove that since the use of maize this section had suffered from pellagra. Thouvenel,[1] who seems to have accepted the idea of the effect of atmospheric conditions on the corn, found more followers in the large cities and this was especially true of those who had studied the question. Many opposed this view from the beginning. The most remarkable observer of this period was Franzago, who for many years was an advocate of the maize theory but gave it up until later in life, when he returned to it and spent the last days of his life disputing with Marzari about the priority of

[1] Thouvenel, "Traité du Climat d'Italie," 1778. Quoted by Roussel.

their respective claims. However, Franzago did not consider maize unhealthy but merely an insufficient form of nourishment. He dared not, therefore, claim that maize was the sole cause because he did not observe the same condition in the cities and yet the same food was eaten there as in the country. He thought it was associated with the consumption of other foods as well. Marzari had observed pellagra in Trevesan for twenty years and held to the maize theory as one would to a religious belief. He [1] said that the appearance of the disease was preceded by the constant use of maize. The long winter preceding the outbreak of the attack when maize was oftentimes the only food to be procured by the poor was in his opinion the only cause worth considering. Marzari has always been considered the father of the maize theory though he was not the first to advocate it. It should be remembered that the older observers and even his contemporary, Franzago, did not attribute to the spoiled or damaged maize the sole cause of pellagra. Marzari seemed to have regarded the noxious substance as a toxin of the same general character as ergot and to have classified pellagra with ergotism. In his writing on this subject he noted that the Turkish wheat (maize) was often picked before ripe and allowed to become moist or stored in the undried state. The grain was made into polenta without salt. The consumers of this food ate only the smallest amount of vegetable food such as cabbage. He also emphasized the fact that maize did not contain a sufficient amount of gluten. His observations were made in the sub-Alpine region. It is the general opinion that Marzari found the noxiousness of the corn in this deficiency of gluten, but a more careful perusal of his work has caused me to conclude that he also suspected a toxicity as mentioned above. All of his contemporaries attacked his position and the Congress of Medical Societies in 1859 approved the position of his opponents. Marzari's work resulted in the division of the students of pellagra into the "zeists" (from *Zea Mays*), or those of his view that maize was the sole cause, and the "anti-zeists," or those who opposed it. It is a notable fact that as late as 1874 the Royal Institute of Sciences of Lombardy officially

[1] Marzari, "Essai Medico-Politique," 1810.

opposed this teaching of Marzari which had been greatly enlarged and developed by Lombroso.[1]

Guerrischi in his memoirs is said to have given Marzari the first idea of the actual toxicity of maize.

This view of maize being responsible for pellagra soon spread from the sub-Alpine country to all parts of Europe where it was used as a food. As early as 1846 Trompio classed those who grew it as enemies to agriculture. About this time Bonafous, a writer on medical and natural history subjects, claimed that he sought in vain for pellagra in the Landes, in the south of France, and in all the territory where Hamean had described it. His inference regarding the etiology was that there must be some other cause than the type of agriculture and the kind of food eaten.

Roussel was very emphatic in the statement that pellagra existed only in those countries where corn is eaten and never attacks those who do not eat it. His observations regarding the history of maize in Europe are worth referring to at some length. He concluded that maize was unknown in Europe up to the end of the sixteenth century and never became naturalized or counted of great importance. During the sixteenth and first half of the seventeenth centuries it did not occupy any place of importance in the countries where pellagra occurred. In Spain in the seventeenth century it gradually replaced millet, barley, and other grains in those rural districts where *Mal de la Rosa* had been found. Chief among these places mentioned was the Asturias, where the disease was first described by Casal in 1735. In France he discovered that maize was known about the sixteenth century but it did not become an important food until the end of the eighteenth century. In Italy he said that after much research he was able to determine that maize did not play any important rôle until after the first half of the sixteenth century. Toward the end of this century and the first half of the seventeenth the disease began to prevail in Lombardy

[1] Lombroso, C., "Die Lehre von der Pellagra," Deutsch. Versuch. von Hans Kurelle, Berlin, 1898. See also bibliograph of Lavinder and Babcock's translation of "La Pellagra," by A. Marie, p. 393, and the Index Catalogue of the Library of the Surgeon, Surgeon-General's Office, Army Medical Museum.

and the Venetian provinces, from which regions it penetrated to the Italian Tyrol. About the middle of the eighteenth century maize produced a sort of revolution in foods among the people of many districts, and during the second half of the eighteenth century this very general use of maize in place of the other cereals extended almost to the northern confines of the peninsula. It has been shown that the general extension of pellagra was first noted about the time of this popularity of maize in Lombardy and in Venetia several years later. The actual date of the general invasion of Lombardy was 1771. In 1845 Balardini wrote a work on the condition in upper Italy and his views and experience coincided with these of Roussel. The latter writer seems to have carefully studied the geographical distribution of both pellagra and the cultivation of maize. He said that he found that pellagra under many names extended over large areas in the temperate climate of Europe between 42° and 46° C. and always reached to the very limits of the area planted in the "American cereal." To the north of this zone Roussel said that he could show that the disease did not occur. In the middle of this zone extending to the warmer climate where maize culture is more perfected and the grain is allowed to become perfectly ripe before harvested, pellagra became gradually rarer as conditions gradually improved until finally it was not found at all in those districts where maize reached the highest degree of perfection. This report of Roussel would appear at first thought conclusive, but a further study of the case weakens his contention. Probably no student has ever so thoroughly combated this statement as Sambon.[1] Among his many excellent examples of error he mentions that Conti, Chief Medical Officer of Ravenna, stated that pellagra was not confined to the small mountainous region in which maize was eaten, but that it occurred also in the district of Lugo where maize is not used. To prove the correctness of this diagnosis he suggested that a new examination be made using Gosio's methods, not excluding the test with specific precipitines. Sambon [1] states emphatically that the topographical distribution of pellagra does not coincide either with the distribution of maize culti-

[1] Sambon, L. W., Progress Report, 1910.

vation or with that of maize consumption. There is much that might be said on both sides of this question. Sandwith,[1] after finding pellagra in Egypt, attempted to determine if it also occurred in the United States, the real home of the grain, but his inquiries were all replied to in the negative. At this time this was interpreted by some as a proof that maize could not produce the disease. It should be remembered in this connection, however, that this grain is at home in this country and does not reach the same state of perfect development in any other land. Again, it has been shown that there is a probability that pellagra has existed here for many years. The patients who have been under my care almost invariably give a history of eating maize in some form for the reason that any one in the south who does not eat corn bread, hominy, or some other of the many delicious southern dishes made from maize, is counted a very peculiar person. These people who give this history of maize consumption never eat it exclusively as do the Italian peasantry but they can never deny the fact that they do eat some daily. It has been exceptional to find a patient who ate maize exclusively. In those afflicted I have made it a rule to absolutely exclude corn from the diet for all time thereafter, but it has never affected the recurrence of the erythema in the next spring. On the other hand I have seen patients who refused to give up the corn bread and the erythema was apparently not affected by this persistence. I have seen recoveries in those who did not refrain from the use of maize. Neither of these facts furnishes any conclusive evidence; they are merely suggestive.

According to Roussel there was not a country affected by pellagra which did not also suffer from poor maize cultivation. He illustrated one of his points by the report of Zantedeschi to Balardini, in which the fact was brought out that pellagra cases occurred in large numbers from 1804 up to 1816 when it disappeared, due to the fact that the high prices of maize forced the poorer classes to use potatoes and vegetables in place of it. In 1819 there was a decided fall in the price of maize and pellagra reappeared and has persisted from this date. Because *flema salada* occurred in a sec-

[1] Sandwith, J., Trans. Nat. Pell. Conference, 1910.

tion where there was no corn to explain the cause, Roussel thought to disprove its identity with pellagra. As mentioned above, the same thing was done regarding the question of the condition known as pseudo-pellagra of Billod. As before mentioned, if this pseudo-pellagra is not pellagra, then the disease in the southern states which has caused such consternation is not pellagra, for the description of this false pellagra of Billod is absolutely the same clinical entity as our pellagra, and I might go a step farther and say the same for the descriptions of the Italian and French disease. One can hardly fail to sympathize with Sir Patrick Manson's rather contemptuous remarks about true pellagra in a consumer of maize and false pellagra in one who did not eat this much-abused American cereal.

There soon grew up among the zeists two schools or, more correctly, two subdivisions of this school. One thought that maize was an insufficient food and the disease was one of malnutrition, while the other school attributed the cause to a fungoid growth on the maize. This growth was known as *verderame* or verdet and was thought to be due to the action of the sporisorium maidis. This was the opinion of Balardini, but it was through Costallat that this doctrine was advanced in 1857. He considered pellagra a slow form of poisoning due to this verdet. This parasite was first found in the markets of Bagneres-de-Bigorre. Experimental demonstrations were made by Balardini, Ellia, and others using maize containing the verdet or polenta made from it. Chickens were fed on it and manifested a number of symptoms which were thought to resemble pellagra. At first there was loss of appetite followed by loss of weight, droopiness, tremulousness, and great thirst. At the end of twenty-eight days the last stage is reached in exhaustion, soon followed by death. Ellia demonstrated that there was roughening of the skin and a furfuraceous desquamation. Lussana and Frua injected into the veins of dogs and birds meal made from maize which contained verdet. In one experiment the aqueous extract was used, in another the powder itself of this damaged grain. The resulting symptoms were dyspepsia, coagulation of the blood, pulmonary ecchymoses, vomiting, congestion of the liver, and

intestinal inflammation which were attributed to the severity of the experiment, but such was not thought to be sufficient to explain the " apathy, clonic convulsions, and paralysis, more or less complete, especially of the hind legs, which are observed in the dogs that, for a time, survive the initial intravenous injections. These phenomena show characteristics too marked to be misinterpreted." [1]

It was through this work of Balardini that the idea of the so-called " zeitoxic " school headed by Lombroso had its origin.

The view that the cause consisted in the insufficiency of the nutritive property of maize was not abandoned without a struggle. The advocates of this theory thought that through its deficiency in nutritive elements there was an interference in the neuro-muscular repair following insufficient protein alimentation. This theory differed little from the idea of Marzari in the insufficiency of the gluten in maize.

The question of the insufficiency of maize as a food may be dismissed with a word. All the recent investigation of its food value has shown conclusively that it is second to none in this respect. Snow of the United States Department of Agriculture (Report 49) says:

" The growing of maize is not only the most important branch of our arable agriculture, but it forms the foundation upon which rests a large part of our wonderful rural development. About 96 per cent of our crop is annually consumed in this country, and more than 80 per cent never crosses the lines of the county in which it is grown. It is the great American crop. On the farm it feeds the working animals, fattens the beeves and hogs, is an important constituent in butter and cheese production, and forms part of the family ration. It appears on the table in American homes both as meat and bread, and again in the form of tempting and appetizing delicacies skillfully prepared from some of its many products. . . . Its value as part of the soldier's ration is appreciated in this country, where the ration established by the military authorities include for bread ' 18 ounces of soft bread or

[1] Marie, A., " La Pellagra." Translation by Lavinder and Babcock, also in Roussel's work.

flour, 16 ounces of hard bread, or 1 pound and 4 ounces of corn meal.' The value of corn meal as a constituent of the army ration was demonstrated practically during the War of the Rebellion. The larger portion of the bread used by the southern armies was from corn meal, while at the same time it furnished a large part of the food supply of the Federal forces. Its value here received the most crucial test which could be applied possibly, and the wonderful strength and endurance shown by the combatants on both sides is sufficient evidence of its value."

The earlier literature on the maize theory of the etiology of pellagra is so voluminous and there is so much of experimental work to be considered in connection with the experimentation of Lombroso and his followers, that it is not possible to deal further with the development of this maize theory though its interest and importance are fully recognized. The history of the development of this idea is a good account of the development of modern laboratory technique.

Cesare Lombroso was born of a Jewish family in 1836 and died suddenly in 1909, after spending the last twenty-five years of his life in the study of the etiology of pellagra. His work on pellagra was begun in 1872. One of his biographers [1] has charged him with an exaggerated tendency to refer all of the mental facts in his work as a psychiatrist to biological causes, and also a serious want of accuracy and discrimination in handling evidence. In spite of this his work marked an epoch in the study and management of criminology. There are many who have the same criticism of his pellagra work as that mentioned of his psychiatric work. But in any event the fact should not be lost sight of that he gave of his time and wonderful experience in mental diseases for the amelioration of one of the greatest scourges of modern times, from which his country suffered more than any other. Time may prove that there were many errors in his conclusions, but in spite of any subsequent developments the name of Lombroso will ever be interwoven with pellagra.

[1] Encyclopedia Britannica, Edition of 1911.

The study of spoilt corn has occupied the attention of many since the beginning of Lombroso's work though it should be remembered that in the time of Hameau there were chemical studies done with the same idea in mind.

Corn [1] has been repeatedly shown to be very subject to various deteriorations because of the large amount of fat contained in the embryo and also because the embryo is so poorly protected from accidents, lying as it does on the surface of the kernel hardly covered at all. The mass of perisperm which lies around the embryo is often changed into a kind of detritus and in its place there is a cavity in which may be found a coleoptera or mite which has been suspected as the indirect cause of the disease by making a place of refuge for the disease organism whatever it may be. When the kernel is diseased there is atrophy of the embryo which does not fill out the usual space between the perisperm and the hull of the caryopsis. This unoccupied space again is supposed to be a source of danger by making an excellent site for the growth and development of fungoid organisms. On gross examination spoilt corn is distinguished by its cracked or wrinkled hull, its tawny gold color, by an absence of luster, and by an enlargement of the embryo which assumes a dark color. There often occur on the exterior of the kernel brown spots or green areas which suggest verdigris and which strongly contrast with the normal white color which the grain should have. Sometimes the grain has the ordinary appearance, but closer examination reveals eroded spots scattered over the surface of the kernel which again favor the entrance of moulds. The growth of this mould produces a green powder which is sometimes confused with the acarus farinæ, but the latter can be easily distinguished by its movement. The meal of spoilt corn is readily detected by its tawny yellow color. Sometimes this color is a gray-

[1] This portion of the chapter is gleaned with slight change of original text from the translation of "La Pellagra," by A. Marie. This translation was made by Lavinder and Babcock in 1910. Marie's work was a synopsis of the Italian work of Lombroso but to be absolutely accurate the translators have compared their translated work with the original text of Lombroso. Acknowledgment is hereby made to the translators for their good work and for my indebtedness to them. E. J. W.

ish brown. There is an aromatic odor and a bitter taste. It is said that good meal when rubbed in the hands gives the odor of polenta, but if bad the odor is mouldy. This would hardly commend itself as a reliable test of so important a matter. It is further recognized that these peculiarities would occur only in the event of advanced deterioration.

When the kernels of spoilt maize are digested in 90 per cent alcohol the grayish yellow color becomes an intense red and the alcoholic solution takes on the same red color which deepens with time. Such change does not take place if the grain is sound, and after several months the only change is a slight lemon yellow color of the alcohol. The red color was not found by Babes and Sion in Roumania and was not observed by Marie except in artificially spoilt maize.

When maize is treated with a dilute solution of caustic potash, if deteriorated, the hulls become reddish brown and later the solution becomes brown and has a very characteristic odor. The color is said to change more rapidly if the degree of spoiling is great. When this alkaline solution is neutralized with tartaric acid, flakes resembling coffee in color are precipitated which have the odor of spoilt corn. This precipitate is insoluble in water and ether but soluble in alcohol.

Lombroso found that the tincture of spoiled corn contained three substances. The first was a ruby red liquid which had a strong, bitter taste and the odor of spoilt maize. This substance was soluble in ether and alcohol, but insoluble in water. It became resinous when exposed and did not yield a precipitate with the iodide of potassium. This tincture contained the oily portion of corn. It was colored by a red substance which can be isolated from the ethereal solution by potassium hydroxide. With this latter substance and benzine it yielded a bright yellow precipitate and a drop of it on paper made a grease spot. This was designated the red oil of bad maize and will be referred to by that name.

The second substance was called by Lombroso pellagrosein and was the toxic substance about which much will be said later. This

substance was reddish brown. It was styptic and very bitter. It was soluble in ordinary alcohol but a yellow precipitate was produced by absolute alcohol which was dissolved by adding a small amount of distilled water. A yellow flaky precipitate was produced by the chloride of platinum. Sulphate of copper produced a green color and at the end of a certain time a reduction of protoxide took place. It was soluble in acetic acid and a solution of potassium hydroxide, and was precipitated by sulphuric acid. When it was treated with water it separated into two parts. One of these, which was soluble, was precipitated in the form of a brown amorphous powder. The other was soluble, producing a bright yellow solution. This latter was the pellagrosein.

The third product was the resinous substance of diseased maize. This substance when heated with ether was solidified, and on exposure to the air became quite hard. It was soluble in caustic potash and in dilute alcohol. It was insoluble in water, benzine, and absolute alcohol. Heated it became semi-solid and could be drawn out in strands like sealing wax. It burned with a white flame, and the odor was said to resemble that of burnt polenta.

The tincture of sound corn produced three substances. The first was not red but amber. It was soluble in ether and did not have the strong odor of the red oil of spoilt maize. It had all the properties of the oil of corn and none of the diseased product referred to above. The second was also yellow. It did not form a precipitate with iodide of potash nor with absolute alcohol. Caustic potash and sulphuric acid produced a precipitate soluble in ether. It resembled the resinous substance of spoilt maize. Substances isolated from damaged maize, according to Marie, were chemically analogous to those isolated from spurred rye, and if these toxic substances from maize were given over a long period in small doses the results were the same as those of ergot given in the same manner. The chemist, Erba, who worked with Lombroso, perfected the method of extracting the various chemical substances above mentioned. In casks filled one third full of water he added a large amount of sound corn. This was shaken daily and examinations made. The grain passed slowly through

acetic, alcoholic, lactic, and putrid fermentation. It was then dried. The kernels preserved their usual form but took on a dirty yellow color, while the embryos were intensely yellow and contained more oil than usual. This grain was found to be easily pulverized. There was an abundant growth of a number of moulds including the aspergillus, the eurotium herbariorum, and the odium lactis.

The maize was then dried until it had decreased in weight 24 per cent. After grinding, the meal was treated with 40 per cent alcohol to extract the soluble substances. This tincture was distilled on the water bath and the residue contained an oily substance called oleoresin of spoiled corn which was analogous to the red oil, a substance which was identical with the alcoholic extract or pellagrosein, a resinoid substance called the glutinous substance of spoilt maize, and finally an aqueous extract.

It was shown that corn bread moulded and allowed to spoil up to lactic fermentation contained a considerable amount of fat which remained solid at 19° C. Sound corn did not yield as large an amount of this oil. Brugnatelli analyzed the oil and the alcoholic extract of spoilt maize and found a bitter, nitrogenous substance which gave the reaction of an alkaloid resembling strychnine. It was a notable fact that this alkaloid was not found in sound corn.

Penicillium glaucum is found in all spoilt grain according to Marie.[1] It forms the greenish-blue dust which is found on most of the kernels of damaged maize. It does not remain on the surface but penetrates into the interior when corn is placed on the ground in winter or while fermenting in damp granaries.

The best known parasite of bad maize is the sporisorium maidis. It has a green color and is found in the furrows of the embryo. Under the microscope it resembles little globules united by fine filaments but easily separated by rubbing. It is a hypomycete. Balardini and Cesati were the first to describe it. They were able to produce in man by its use gastritis and diarrhea. In chickens

[1] Marie, A., "La Pellagra," 1909, and Lavinder and Babcock's translation of the same, 1910.

it caused loss of feathers, decided loss of weight, and droopiness. It was supposed to have no important connection with pellagra because Lombroso was able to find only three specimens in Lombardy during many years. The large number of moulds mentioned by Marie are not of sufficient interest or importance to justify mentioning at this time.

The bacteriology of damaged maize has been carefully studied but the results have been by no means uniform. The commonest of these is the bacterium maidis which is morphologically identical with the bacillus mesentericus vulgaris. It is a small cylindrical bacillus which is very motile, growing in chains of two or three organisms. It stains very readily in nearly all the usual laboratory stains, but especially in an alcoholic solution of methyl violet and the usual aniline dyes. It is said to resist a temperature of 90° C. and grows luxuriantly at from 25 to 30° C. This organism is found in many specimens of meal and often in pure culture. Marie said that this organism, which cannot be distinguished from the potato bacillus, was found in large numbers in freshly baked bread. When this bread was placed in a damp chamber, at the end of ten days it showed numerous yellow and blue colonies which were found to be composed of a large variety of organisms of too little importance in the work before us to justify enumerating. The only one of these organisms of any importance seems to be the bacillus maidis, which has been found in sound meal. In 1881 Majjochi found a very motile bacillus in sound corn as well as in the diseased, though in the latter it was always much more abundant. He reported that he thought that it was this same organism which he found in the blood of seven pellagrins early in the disease. Cuboni found it constantly on spoilt maize and he recognized its marked similarity to the bacterium thermo, though it resisted a higher temperature. Marie constantly referred to the bacteriology of corn shipped by water and the various effects of sea water on the growth and distribution of the various organisms in the kernel. All of this will be passed over in this work because it can have no bearing on the situation in the United States as all maize in this country is shipped by rail. Cuboni

said that the bacterium maidis occurred in damp corn and especially if the corn was immature, and that dryness arrested the development but did not destroy it, hence corn well dried can later become spoilt by this organism in the presence of moisture. This organism resists a temperature of 100° C., hence it would not be impossible to recover from polenta the living bacillus. Its growth on gelatine causes liquefaction and in the test tube the growth assumes a funnel shape. Coboni's work on the feces of pellagrins and healthy individuals showed that in both classes the organism was present but that in the pellagrin the number was larger. He said that when taken into the intestinal tract in spoilt polenta the organism multiplied very rapidly and caused a true intestinal mycosis.

Peltauf and Heider studied the same bacillus and identified it with the potato bacillus. They found it to be the inhabitant of the intestinal tract of fifteen pellagrins, but its presence there was not regarded as pathologic. The bacillus was an aërobe, it was motile, and it produced spores at one end or in the middle. I have done a great deal of work with this organism and am convinced that it is harmless and in no way connected with pellagra as a causative factor.

Heider in Ludwig's laboratory studied the chemical products of the life of the bacterium maidis and concluded that at a high temperature this organism could, in the presence of moisture, bring about changes in corn. Recent experimentation demonstrates that in polenta it resists the temperature counted sufficient for thorough sterilization, but after repeated sterilizations under high temperature it is destroyed. Grown in the incubator on polenta after three days it produces a strong odor of mice. Marie concluded that its action was indirect, acting as did the oidium lactis in producing a toxic substance from the parenchyma of the grain. Peltauf's animal experimentation by the subcutaneous injection in rabbits, guinea pigs, and rats was entirely negative except in so far as it was proven that the organism was not pathogenic. But when he infected the alcoholic extract of corn meal with this organism and allowed it to stand for three months, he was able to

produce coma, paralysis, and death by the injection of the product. Cultures of the potato bacillus in polenta produced the same results which proved the identity. Heider and Gorizia removed from spoilt maize a substance giving the reaction of an alkaloid which killed rats after producing anesthesia and narcosis.

These experiments were repeated on a larger scale by Lombroso and others with the following results.[1]

"If cultures on polenta of one, two, six, and up to seven days old, are given to animals they become accustomed to it slowly; the initial diarrhea, which is the only symptom, may even cease; the cultures over four or five days old are refused, perhaps because of their bad and very pronounced taste.

"As a consequence of this nourishment, digestive troubles are produced, sometimes vomiting, almost always diarrhea, but never derangement of the sensibility or of the motor system. At the end of some days the weight begins to diminish, but then maintains itself within normal limits. The temperature is usually maintained at normal; in the first days only two cases showed a slight evening rise.

"The attempt to cultivate this bacillus on wheat bread met with little success; two dogs fed for fourteen days with this bread showed no change.

"An experiment was then made with the alcoholic extract obtained from a culture on polenta twenty-five days old. The extract, prepared by Professor Fileti, was injected into three dogs under the skin of the back in doses of 5 per cent, 10 per cent, and 25 per cent of the weight of the animal. The two dogs which had received the largest doses died two days later, after presenting the following symptoms:

"Paresis of the hind legs, almost continual tremor, general depression, which was rapid and progressive, gradual loss of voluntary motion, complete paralysis of the hind legs, mydriasis, slight increase of temperature, acceleration of respiration and pulse, insensibility, bloody diarrhea, and death with prolonged

[1] From Lavinder and Babcock's translation of Marie's "La Pellagra," which was a synopsis of Lombroso's work.

agonistic state. At the autopsy, edema of a hemorrhagic nature in the hypogastric region, extravasations in the spleen.

"The dog inoculated in the proportion of 5 per cent of its weight exhibited at the beginning the same symptoms, but at the end of the second day his condition improved; however, the hind legs remained paralyzed and the diarrhea continued for several weeks with a remarkable diminution of weight.

"In the case of two other dogs, intravenous injection in the proportion of 5 per cent of body weight caused death after the development of the above-mentioned symptoms.

"Injections into ten frogs, with corresponding doses brought on death in three hours with paralysis, diffuse ecchymoses on the interior of the thighs and in the hypogastric region. Intravenous injections of the extract of sound polenta up to 10 per cent had no evil consequences; the same may be said of the subcutaneous injections made in double doses."

The final conclusion of Lombroso was that pellagra was an intoxication disease which was produced by the action of certain organisms on maize. These organisms in themselves were harmless but possessed the property of producing a poisonous ptomaine when they came in contact with the kernel of the maize. From the above-mentioned experiments it is plainly seen that the bacillus maidis cannot be counted pathogenic. It is not so harmful even as the bacillus coli communis, which when placed beyond its normal territory in the animal economy becomes at once pathogenic. Not so much can be said of the bacillus maidis because it can do no direct harm. It is accused of being one of the ptomaine producers, but opinion is not altogether united on this matter. Lombroso and Peschel thought it was active in the decomposition of albuminoids and hydrocarbons and that it might possibly be counted an intestinal irritant. It is important to consider that this bacillus is found in the best grade of sound maize and in the normal intestinal tract in which latter place it is known as the bacillus mesentericus vulgaris. Efforts have been made to recover it from the blood of pellagrins but it cannot be done. For two years

I made routine blood examinations of every case of pellagra which I saw and in all stages, but the bouillon invariably remained sterile. Cuboni made thirty attempts in cases of pellagra and his results were also negative. The same negative results occurred in the skin lesions and intestinal tract of dogs supposed to have the disease, while animals fed on the tincture of spoilt corn with all organisms removed were supposed to develop symptoms of pellagra. It is not my opinion that this condition was pellagra because I have never been satisfied that the disease can be experimentally produced even in the presence of such testimony as that of Lombroso and Marie above recorded. Lombroso always emphasized the fact that in order to produce pellagra it was necessary to feed the animal for some time on the toxic products of deteriorated maize. This idea owed its origin to the fact that spurred rye does not cause ergotism from one or two exposures but by a constant repetition of the poison. Tuczek,[1] who made a careful study of a series of cases of pellagra and ergotism, thought that the two diseases belonged to one class, grain intoxication. There are many objections to the classification of pellagra with ergotism but the one which is most logical is the pathologic basis. Even Marie is forced to acknowledge that the pathology is not of such a character as ergotism but points to a parasitic cause. Sambon's work on this phase of our study is most important and will be referred to at length later. It is reasonable to classify this disease on a pathologic basis because the etiology is in doubt, and if such a classification is made it will place pellagra in that group of diseases with trypanosomiasis, kala-azar, and Rocky Mountain fever. This pathologic condition is a round cell perivascular infiltration of the tissues. In addition to this there is an increase of the mononuclear elements of the blood which is equally characteristic of a disease caused by an animal parasite.

In a large number of cases it has been my rule to enter on the case record the character of the food eaten and I have been struck by the fact that usually the reply is that the patient did not eat

[1] Tuczek, F., "Klin. u. Anat. Studien ueber die Pellagra," 1893.

much corn food, and then it was usually hominy or grits which is not so apt to become deteriorated nor is it eaten half raw as is so often the case of corn bread. I have had patients with pellagra who had never eaten any corn food at all. One of my fatal cases said that when he was seven years old his father told him that if he would eat one piece of corn bread he would be rewarded by a visit to Robinson's circus. This was the only time in his life that he ever ate maize in any form, but even the most ardent zeist could not deny the fact of the case being one of pellagra. In meeting this argument a zeist confrère, who had acknowledged the correctness of the diagnosis, suggested that the wheat flour might have been adulterated with corn meal, so I investigated this possibility with the result that I found that he ate flour from his own mill and that he knew that there was no adulteration. This same zeist thought he had solved the problem in the discovery that the patient drank corn whisky for which North Carolina is more or less famous. On investigating this point it was learned that the patient did not drink corn whisky until after he became a victim of pellagra. In this connection it might be well to say that alcohol is a decided predisposing cause of pellagra and in my series it was the rule for male patients to be alcoholic.

It is exceedingly difficult to argue this maize theory of pellagra in the southern states with any fairness to the anti-zeist side of the question for the reason that a native-born Southerner seldom goes through the day without eating maize in some form. It largely holds the place in this particular section which is held in other sections by wheat. Every southern home has boiled hominy or grits for breakfast with the same regularity that the Scot has oatmeal. In addition to this unvarying dish there is often added corn meal muffins for the breakfast bread. For the mid-day meal, corn bread is a common dish, and for the evening meal it is exceptional for some dish made of maize to be omitted. So it is readily seen that there is small chance for a Southerner to escape maize in some form, and as a general proposition it may be said that all the inhabitants of the southern states eat maize in some form at least once daily. This makes it impossible for any one to say

absolutely that corn meal could not have played some part in the causation.

Marie argues that in no parasitic disease is there the same amelioration after change of food as in pellagra. In reply to this I can say with as much positiveness that the same wonderful change is often brought about in my patients without any change of food at all and by the use of arsenic in the form of atoxyl. I have in my mind a young woman who has gained thirteen pounds in the past six weeks by the atoxyl treatment without any other change in her manner of living. I have seen a laborer recover without changing his food, place of abode, occupation, or anything else that could have any bearing on the disease. On the other hand, I have seen relapses in patients who had apparently recovered and who had not eaten maize in two years. It is important to know in considering this question that the rich and the poor alike in the southern states buy the same quality of corn meal from the same barrel and are subject, therefore, according to the terms of the corn theory, to the same condition. Pellagra has appeared in sections of North Carolina where the maize has been raised by the people for a century or more in the same manner as now employed and ground in the same old-fashioned water mills. In such localities I have been unable to discover any change in the manner of living during the past half century, especially in those settlements far removed from the railroads. How can maize play a part in the causation of the scourge which in some instances has taken off a considerable percentage of the whole population? Why should the same thing not have occurred long ago if the maize was at fault? Such questions cannot be answered by the zeists. For the sake of argument suppose it is granted that these people have only recently begun the use of corn meal from the great corn states of the West and that the disease has entered in this way. It is a notable fact that the maize grown in the West is far superior to that grown in the South, and at first glance it will be seen that the dryness of the West would be more favorable for keeping this grain in a perfect state than in the South where the humidity is greater. It is true that bad corn is often received in

the South from the West, but there is no one thing in which the American merchant is so proficient as in detecting such corn and in claiming indemnity from the railroad companies which are responsible for the delivery in good condition. Some might argue that this corn is never destroyed. That is true, but it is equally true that it is never eaten by man. It is usually sold as chicken food that has been known to kill fowl and cattle, but I have never seen any similarity between this acute grain poisoning and pellagra.

Marie said that in 1883 the maize crop of Mazze and of Vischi was destroyed by inundation and by hail. Some of the grain was bought and examined by Gibelli and Mattirolo who found the aspergillus, the rhizopus, mites, and the bacillus maidis. This damaged grain with other food as milk, meat, and wheat bread was fed to dogs and chickens. In spite of the mixed feeding there was a loss of weight in the dogs which began from three to twelve days after the commencement of the use of the maize. There was also a rise of temperature coincident with the loss of weight which was attributed to a toxic pyrogenetic substance contained in the grain. There was some reduction in the red blood cells but this anemia was not constant. It was shown by this that nourishment with spoilt maize does not cause chronic inanition because in such a state there is a constant decrease of red blood cells. Two of the dogs showed an increase of red blood cells.

There was frequently present tonic muscular spasm and increase of the tendon reflexes. In two dogs the tetanic condition was very marked. The inconstancy of this phenomenon was admitted. In seven out of ten there was a pronounced torpor of the muscles; in six, a cerebral torpor; in three, loss of sensibility; in four, muscular tremor.

Diarrhea was said to be more pronounced than in man and was often preceded by refusal of food and dysphagia.

The erythema was observed in only one case. This dog remained free from anemia, torpor, and spasmodic phenomena, and it was noted that the sitophobia and paresis disappeared with the appearance of the erythema.

Marie's [1] conclusions are given thus:

"To sum up, we can say that in dogs pellagra shows itself sometimes under the anemic form, sometimes under the spasmodic form, and sometimes under the cerebral form, which is precisely analogous to the pathologic anatomy and symptomatology of pellagra in man, in whom it is erroneous to speak of pellagra in general and is more didactic than scientific to make divisions into first and second stages. A more accurate division would be into anemic, spastic, tabetic, cerebral, and other similar forms of pellagra.

"Nutrition with bread from moulded corn calls forth the same symptoms as nutrition with the grain or meal of moulded corn. If it never causes true tetanic phenomena, it is, however, accompanied by rigidity of the lower extremities, with exaggeration of the tendon reflexes — symptoms more characteristic of pellagra. Later, cutaneous erythema, the most typical symptom of pellagra, shows itself distinctly. This was lacking in other experimental animals, although it is known to occur in 'enmaizados' horses in Mexico, in which it is notable that stupidity and dysphagia appear shortly before the erythema, and disappear with its advent. And this is in wonderful accord with the observations of medical practice which tend to establish an antagonism between the nervous phenomena and the skin symptoms. Perhaps localized hyperemia acts as a cutaneous revulsion — one sees nervous diseases modified by the employment of a strong irritation of the skin. In general the symptoms are more benign in animals fed on mouldy bread.

"In twelve chickens fed on spoilt corn convulsive phenomena were exceptionally noted, and if a complete marasmus could be excluded, the spoilt grain alone produced increase of weight, but finally death intervened after atrophy of the feather follicles, with changes in the skin and horny appendages. A fact worthy of remark is that chickens entirely tame for months became very wild at the end of five or six months on the regimen of corn; they

[1] Lavinder and Babcock's translation of Marie's "La Pellagra."

fought their companions and had to be shut up. Another chicken had photophobia and was unwilling to leave the cage.

"Taken all together, the disease was less pronounced in the chickens than in the dogs; however, the chief effects of nourishment with spoilt corn, especially the cutaneous symptoms and muscular disorders, showed results analogous to those of the subcutaneous injections of extracts of oil and of other preparations of spoilt corn.

"The proof seems, then, to be regarded as established, that in pellagra the chronic poisoning does not come from microbes infecting the animal organism, but from the chemical transformations of the parenchyma of corn; and since the more important toxic substances pass into the tincture made from the grain, it would seem wise and profitable to study experimentally the action of this tincture. This would seem all the better since the tincture is very well adapted for administration to human beings."

The fact has not been established from these experiments that pellagra was the condition produced. It is acknowledged that in only one dog was there an erythema. In man we do not dare to diagnose pellagra without the skin manifestations, hence it does not seem reasonable to expect the diagnosis to be accepted in the lower animals without the characteristic skin manifestations. There are many other conditions which could be equally well attributed as the cause. As said before, it has never been proven that any of the lower animals are susceptible to pellagra.

Lombroso and Dupré found that the glutinous and resinous substances from maize produced no effect in man or the lower animals. The toxic substance which was pellagrosein when given to dogs produced droopiness and diarrhea and in man it caused torpor, anorexia, and nausea accompanied by diarrhea. It was said that with care a toxic action on the lower animals could be produced by pellagrosein.

The following experiments were made by Lombroso[1] and counted by him conclusive evidence of the correctness of his claim.

[1] Lavinder and Babcock's translation of Marie's "La Pellagra."

"In frogs clonic convulsions appeared half an hour after the injection of pellagrosein in a strong dose of 50 centigrams. At the end of an hour there were increased motor reflexes and sensible diminution in the cardiac pulsations. Two hours later the movements of the heart gradually diminished and a tetanic state supervened which increased till death. In other experiments it was noted that at the end of a quarter hour the frog took a vertical position in the water. If placed on its back it did not turn over, and displayed fibrillary contractions of the lower limbs; at the end of a half hour complete narcosis appeared; after three-quarters of an hour anesthesia to the strongest stimuli; one hour later tonic convulsions, very much increased reflex excitability, and a pronounced tetanic state; three hours later death. A very small frog after an injection of 5 centigrams died immediately.

"In a great number of experiments there was found very notable differences in results, such differences being dependent upon the size of the dose and the time when the substance used had been prepared, whether in August or in September.

"With small doses a tetanic state appeared in 90 per cent of the cases, especially if the frogs had been placed in lukewarm water. Sometimes this state was preceded by paresis, or perhaps death followed it in half an hour to twenty-five hours.

"In the case of other frogs with doses of 25 to 100 centigrams tonic cramps appeared in all the cases and paresis of the extremities was produced to such an extent that the animals rested vertically in the water. In 27 out of 100 frogs tetanic convulsions with narcosis preceded death which occurred usually in thirty minutes. In the cold months the substances had scarcely a visible effect and even that frequently was evident only on close examination. The influence of the temperature appears distinctly when the animals are kept under artificial conditions in cold or warm water.

"In water at 3° C. a dose of 5 centigrams caused only hesitation in movement and increased motor reflexes at the end of six to twenty-four hours. The same result is produced sooner in water at 8° C.; at 32° or 36° tetanic convulsions with death re-

sulted from even small doses; and also from the blood of animals poisoned by pellagrosein, those injected remained stiff in water at 3° and could not leap; at 32° to 36° they were very lively at first, but soon became somnolent, though they did not die and did not show any tetanic condition; they succumbed, on the contrary, very quickly with tetanic symptoms, when placed in water at 38° to 42° C.

"For animals kept in lukewarm water the minimum lethal dose was 1 centigram per 14 grams of animal weight. The maximum dose without death was 50 centigrams per 12 grams of animal weight.

"In general, chickens showed a diminished sensibility to the effects of the substances.

"In the case of a pigeon, death occurred after a dose of 4 grams per kilogram, with clonic convulsions, preceded by narcosis, somnolence, and diminution of temperature. The blood of this pigeon, still warm, injected into a frog, produced tetanic symptoms. In the case of hawks, death occurred after a dose of 2 grams per kilogram, with diminution of weight, narcosis, and tonic-like convulsions.

"In the case of rats doses of 12 grams per kilogram given internally was without results; on the other hand, the same dose administered subcutaneously produced torpor, anorexia, and paralysis of the hind legs with unilateral contractions; they fell on the right side and when they tried to move they rolled or sometimes walked backwards. Later complete paralysis and notable diminution of temperature. Convulsions appeared in only two rats after the absorption of 2.8 grams per kilogram of the poison. In three others with somewhat larger doses, death occurred at the end of one to thirteen hours.

"The autopsy showed hyperemia of the spinal cord, pia mater, liver, and kidneys, once also of the lungs; in one case softening of the cord was found. In the case of three out of six of these animals, tetanic convulsions appeared, preceded or followed by paralysis. Heat seemed to favor narcotics, as cold did tetanic phenomena.

"An experiment made upon one adult cat only with a subcutaneous dose of 1.4 grams per kilogram of the most active preparation caused death in ten hours. Soon after the injection immobility set in with refusal of food and rigidity of the hind legs. It was only at the end of three hours that there appeared tremor, then tetanic convulsions, hyperesthesia, increase of temperature (2°) and, two hours later, coma. At the autopsy — hyperemia of the brain, spinal cord, liver, and kidneys.

"In cases of dogs the results were also convincing. With doses of 2 grams per kilogram repeated vomiting occurred after a half hour to two hours, also contraction of the hind legs, dilated but mobile pupils, increase of sensibility and of motor reflexes — two hours later general tetanic convulsions, acceleration of the pulse and respiration and lowering of temperature. After each attack of tetanic convulsions the dog loses his equilibrium, crouches on the hind quarters, and presses his head and paws against the ground. Experiments with other dogs gave similar results.

"At the autopsy there was found hyperemia of the meninges, optic thalamus, and of the gray matter of the spinal cord; in one case softening of the lumbar cord; twice ecchymoses of the lungs and congestion of the liver; once only hyperemia of the entire brain.

"It is necessary to distinguish three different preparations made from the oleo-resin of spoilt corn: that of July and August which is very bitter, muddy, chocolate colored, with a strong smell, obtained from the corn carried to the state of putrid fermentation; the oil of September, less colored, less bitter, and having a normal odor, is extracted from corn less spoilt; finally, the oil extracted from yellow bread, which is solid at 19° C., and the oil extracted from the embryos of the grain.

"It was found that in more than a hundred cases in experiments made during the summer with the active preparations, tetanic convulsions appeared at the end of four to ten hours in 50 per cent of them. The dose of the preparation was .75 gram up to 1 gram with animals which weighed between 18 and 35 grams. To tetanic convulsions succeeded paralysis of the hind

legs in 5 per cent, narcosis in 10 per cent; in 30 per cent tetanic convulsions did not occur, but difficulty in leaping and exaggeration of the reflexes of the hind legs at first and later of the fore legs occurred. In 20 per cent only narcosis occurred without spasmodic symptoms, but death always followed.

"The same preparation, in dose of 1 gram for 23 grams of weight, injected into frogs kept in a room at 8° C. in December, produced only mild and retarded symptoms. Tetanic phenomena showed themselves at the end of eighteen hours, and at the end of thirty hours death occurred. Other experiments in cold or warm water demonstrated that the symptoms of poisoning were much mitigated by cold.

"If, before the injection, the heart were laid bare, there was found, as in the use of the alcoholic extract, that at the end of a half hour a retardation of the pulse occurred most marked on the appearance of tetanic phenomena.

"The same tetanic phenomena appeared after injection was made in a rat whose brain had been removed; partial section of the cord prevented spasmodic phenomena on the corresponding side. The members remaining in nervous connection with the rest of the body, but not with the circulation, exhibited constantly tetanic symptoms.

"The urine and blood of animals having had injections of the alcoholic extract as well as the oil, produced tetanic phenomena in frogs, though the animals themselves remained free from toxic symptoms.

"The experiments on chickens are important because of their duration. In one chicken with a subcutaneous injection of the oil there were no motor symptoms; but it was droopy all day and had diarrhea. A cock behaved in the same manner. When given by mouth, this substance had a less marked effect; however, it arrested increase in weight in young fowls. In one untreated chicken the weight increased 200 grams from the 20th of November to the 2nd of December, but under treatment with the oil from the 3rd to the 16th of December the increase of weight was only 100 grams. Finally, after five months of interrupted

administration of the oil, there appeared choreiform movements of the head, previously observed in the experiments with Dupré. In the case of one chicken choreiform movements of the head appeared at the end of ten days; with repeated doses the motor derangement became general — it walked backwards, raised the feet slowly and in an exaggerated manner, and had a tendency to walk very near the wall. Then eczema of the comb appeared with diarrhea, increase of temperature after the injection, defervescence in the intervals; the chicken died with typhoid and paralytic phenomena. At the autopsy were found intestinal hemorrhages similar to those seen in septic poisoning.

"With four rats one dose of 5 grams brought about subnormal temperature with paresis, contractures, and once death following paralysis of the hind legs. A cat, after a dose of 4.9 grams per kilogram, had photophobia and refused food. With larger doses (6 grams) loss of appetite, paresis, decided photophobia and death at the end of two days, with loss of 40 per cent in weight.

"In the case of a bitch, after an injection of 20 grams, tonic convulsions of the legs and paresis occurred in two hours. Three hours afterwards there remained only a decided reflex excitability, mydriasis, agitation, refusal of food, and staggering gait. The next day there remained only difficulty in leaping and walking, with rigidity of the fore legs. In another dog, after an injection of 30 grams, torpor, rigidity of the hind legs, and slight desire for food. In general, the oil produced the same symptoms as the alcoholic extract, although less in degree.

"The oil of moulded bread produced the same symptoms as the maximum grade of oil of corn prepared in August. In a single experiment it was more active."

The oil made from the embryos of spoilt maize caused symptoms similar to those produced by oil made from the entire grain, but the effect was not so marked.

The effect of the aqueous extract was similar to that of the alcoholic extract, but not so decided.

The alkaloid was removed by Erba from the oil. When injected

into frogs it produced tetanic convulsions. Lombroso claimed that the residue after the extraction of the alkaloid still produced tetanic symptoms in the frog and inferred from this that there was more of a poisonous nature in spoilt corn than this strychnine-like product.

Pellizzi[1] studied sound corn meal and found that an article counted of this type often contained more micro-organisms than another appearing much less sound. He thought that to insure a safe food it would be necessary to dry the grain in an oven at 70° C. He concluded that the important organisms of spoilt corn resemble the putrefactive type, because symptoms said to be analogous to pellagra were produced in dogs by such cultures. He thought also that the results could be attributed exclusively to putrid substances and not to a specific poison of spoilt maize. The pellagrous manifestations produced in dogs by the intravenous administration of 10 grams per kilogram of body weight of an aqueous extract of polenta which was contaminated with certain micro-organisms were pareses, gastro-intestinal disorders, and psychic confusion.

Marie concluded his discussion with these significant utterances:

"The facts recognized by statistics and by clinical observation are not always easy to reconcile. The statistics show that only in the case of 25 per cent of pellagrins can it be affirmed with certainty that they were nourished with food consisting principally of corn very badly spoilt. On the other hand, clinical observations demonstrate that it is not rare to see cases of severe pellagra in persons well nourished and in good circumstances, of whom it can be said that they do not habitually eat spoilt corn. Finally, there are recrudescences of pellagra with grave symptoms when the convalescents return to nourishment with corn, even when the corn consumed answers to the most severe hygienic demands.

"These experiments prove the existence of micro-organisms

[1] Pellizzi, G. P., "Sull' etiologia della pellagra in rapporto alle sostanze tossiche prodotte dei microorganismi del maiz guasto." *Ann. di freniat*, Turin, 1893–94, IV.

either in a developed form or in the form of spores in the grain and meal of corn which have the very best appearances and are habitually used for human food. It can then be supposed that the elements necessary to the production of the pellagrous symptoms, once having entered into the circulation, are there decomposed under the action of ferments found in the organism, and undergo, after absorption, toxic transformations. It cannot be determined, according to Pellizzi, what is the nature in a given medium of the products of the bacteria found on corn. Do they constitute a chemical poison in the strict sense of the word; or, as is more probable, do they belong to the amorphous chemical ferments, which can be produced at a determined phase of their development? For many similar ferments complex actions have been found; Pellizzi found them in his extracts of corn. It is reasonable that the harmful effect does not come from a pure culture of one organism, but from a mixed culture of several varieties. It is a question, certainly, of a combined and probably mutual action, not yet defined. If a toxic substance could be directly drawn from edible corn without mixture with putrid substances in the strict sense of the word — then the features of pellagrous poisoning can represent a poly-toxic state. Finally, it is necessary to take into consideration the most complex and various facts and to give to spoilt corn a very wide definition. Almost all corn, with few exceptions, can thus be considered spoilt corn to some degree. Corn, absolutely sterilized, if one could have it, would certainly be harmless, and, of course, the meal also. But if it is difficult to have corn entirely dry, it is certainly impossible to keep it in this state, for as soon as the places in which it is stored reach a certain degree of humidity, the most diverse micro-organisms find favorable conditions for their development.

"In concluding his experimental work Lombroso states that 'with such evidence as has been submitted it does not seem longer possible that the specific cause of pellagra can be doubted, and it is certain that the etiology of other maladies can present documents neither more numerous nor more convincing.'"

Probably no work on the subject of maize as an etiological factor in the production of pellagra has yet been done of so great importance as that of Tizzoni who claimed to have isolated from the blood, cerebro-spinal fluid, feces, and organs at autopsy of pellagrins, a specific micro-organism, called by him the streptobacillus of pellagra. The same organism was also found in certain samples of spoilt maize. This investigation extending over a period of ten years was of the most exhaustive character and bade fair at first to settle the mooted point, but it has not been received with much enthusiasm and there are serious objections made to it. It has been my privilege to verify the greater portion of Professor Tizzoni's claims in my own laboratory in North Carolina. At the outset it should be said that this organism is not the bacterium maidis or potato bacillus, as some American students have seen fit to designate it. The organism was first isolated from the blood of patients with the acute or typhoid type of the disease. In 1907 it was shown that the disease could be experimentally produced in guinea pigs, provided maize was added to the diet; when the maize was omitted the disease could not be produced. The following hypotheses were advanced by Tizzoni:

(1) The germ is the same in both the acute and chronic types of pellagra.

(2) In the acute type the germ is found in the blood where it reproduces itself.

(3) In the chronic type of the disease it is limited to the digestive tract.

(4) The toxins produced in the digestive tract are modified perhaps by the blood serum or white blood corpuscles before reaching the nervous system.

(5) Maize is either a suitable culture medium or acts as a means of transmission of the germ. The germ is propagated by fertilizing the maize crop with the dejecta of pellagrinous animals. This germ is more active when the grain is not properly matured.

This work was based on the acute type of the disease; on

the chronic not enough has been done to draw any reliable conclusions. The author drew an analogy between acute and chronic pellagra and acute and chronic tuberculosis. Acute tuberculosis, he said, was the final stage of the chronic. This conclusion has been proven incorrect in the southern states where the acute form of pellagra has been primary in many accurately reported cases. This was the experience of Searcy in Alabama and was my own experience in North Carolina. Such a condition as this acute primary pellagra seen by us in this country is unknown in Europe where the very word bears the impression of a chronic disease. We must take exception also to the explanation that the grain became contaminated by the organism in question through the fertilization of the maize with animal excreta. This can be readily disproven by the fact that maize in the United States is not so fertilized except in very isolated instances.

Tizzoni's organism was obtained from the blood of animals which had been inoculated with the blood of patients suffering with acute pellagra. This organism can be cultivated indefinitely on defibrinated rabbit's blood by renewing the culture every thirty or forty days. When it is so cultivated the form is very characteristic. Chains are found to predominate. Great variations in size and morphology are noted. The organism is quite small and at first sight appears as a streptococcus, but is really a bacillus, though a very short one; hence the name given by Tizzoni — the strepto-bacillus of pellagra. When transplanted from the rabbit's blood serum to agar-agar or beef broth the chains are found to be made up of larger elements. Often there is an occurrence in pairs and an appearance of a lanceolate bacillus similar to the pneumococcus of Fränkel. At first considerable difficulty is found in growing the organism, but it soon becomes accustomed to saphrophytic life and grows readily on agar-agar while at first it would only grow on non-coagulated albumens.

The most important characteristic of this organism was that it was able to resist unusually high temperatures. A culture in agar-agar twenty-four hours old was obtained from a blood serum culture. Half of it was kept as a control and the other half

was divided and exposed for one hour to 60, 70, 80, and 90° C. respectively. The tubes exposed to 60° and 70° grew as well as the control. The 80° tube grew slowly, while the one exposed to 90° remained sterile. Such a resistance to heat in an organism not bearing spores is unique, though something of the same nature is said to be possessed by the bacterium maidis. It was noted that this culture, which had been exposed to 90° C. for one hour and which would not grow, when injected into a guinea pig would produce death, not by a toxemia but by the growth of the living organism. In such cases the organism which has been exposed to this high degree of heat may be further propagated by passing through the guinea pig, and this is a valuable way of securing a pure culture. Suspected material is heated to 90° C. for one hour and a portion of the heated material is injected into the guinea pig and the pure culture of the strepto-bacillus of pellagra is recovered from the blood. It is readily appreciated that such an organism could easily retain its life in many instances in polenta. This dish of the Italian peasantry is often very imperfectly cooked and it has been shown that corn meal has a property of "balling," that is, of forming masses when mixed with water. Wheat flour does not have this property, but at once when brought in contact with the water forms a homogeneous suspension. It was thought that these polenta balls could easily harbor in the center this organism which had not been exposed to as much as 90° of heat. In one isolated instance death occurred by the injection of a culture which had been exposed to 100° for one hour.

It was shown that in the experimentation with this organism given by the mouth, which is assumed to be the manner in which the infection occurs, the disease could not be produced unless the animal was fed maize at the same time. One group of animals was fed the organism without corn food and remained healthy; a second group was fed the same corn without the organism and remained healthy; a third group was fed the organism with corn food and all died with symptoms supposed to be those of pellagra. It was evident from this that the corn was essential either by

making a predisposition or by furnishing a suitable nutritive medium. It was then tried to see if animals fattened on maize which was later withheld from the diet and then these same animals inoculated with the streptococcus could be infected. Such animals were infected and died in from sixty-six to seventy-two days. The conclusion from this result was that corn predisposed to the disease.

The rabbit was found to be immune to subcutaneous injections and showed only a slight reaction to the gastric method of infection. A slight diarrhea was the only result.

An effort was made to test the property of vaccination with this strepto-bacillus. Robust guinea pigs were subcutaneously inoculated with twenty-four-hour-old agar-agar cultures subjected to 90° C. for one hour. The dose was gradually increased and the intervals varied from five to ten days. The animals were fed ordinary food and the weights increased. But none of these animals were able to resist gastric infection, all of them dying. This experiment at least showed that a tolerance was acquired by beginning with small doses. It was seen that animals which had been vaccinated did not survive mouth infection as well as those not so treated; the former died in a shorter time than the latter. This was supposed to be due to anaphylaxis.

The feces in chronic pellagra was found to contain the organism and it was possible to reproduce the disease in guinea pigs by the inoculation of fecal matter which had been exposed to 80° C. for one hour. In the chronic form the organism was not recovered from the blood as in the acute. It was seen that all diarrhea in pellagra was not specific, but that pellagrins were very susceptible to diarrhea on the slightest provocation, such as a change in food.

Spoilt corn was found at times to contain the same strepto-bacillus and its virulence was greatly enhanced by passing it through the guinea pig as above mentioned. All the tests made with the organism obtained from the grain showed that it was the same as that isolated from the blood in the acute type of the disease. Tizzoni found the organism in nine samples of what

he considered bad maize, but in nine samples of sound maize it could not be found at all. An organism was found in good corn, but it was proven not to be the strepto-bacillus by the fact that it did not resist a temperature of 80° C. for one hour. Should it be proven that this is the specific cause of pellagra, it would be a simple matter to test all corn by this heat isolation process. A portion of the suspected corn by this method is placed in a tube of bouillon and placed in the incubator at 37° C. for twenty-four hours or longer. This gives sufficient time for the development of a sufficient number of organisms. The culture is then subjected to a temperature of 80° C. for one hour and later a culture made from this heated culture will demonstrate the presence of the strepto-bacillus. To be more accurate it is well to subject the corn culture, after allowing a growth to occur, to a temperature of 90° C. for one hour and then, taking a portion of this heated culture and passing it through a guinea pig, to await the development of the symptoms supposed to be pellagrous.

It has never been proven whether or not this organism of Tizzoni can be found on other grains, as wheat, barley, or rye. It also remains to be proven if there is any other way of infection besides the mouth.

Tizzoni showed that in animals which he had infected with his organism he could effect a cure by the injection of the blood serum of healed pellagrins. A group of control animals not so treated invariably died, while all of the treated animals recovered.

The conclusions of Tizzoni were as follows:

(1) The same organism isolated from acute pellagra can be isolated from the blood of chronic pellagrins as well as from the feces. It was also found occasionally in bad maize.

(2) The organism was a non-spore bearer and resisted a temperature of 80° and even 90° for one hour.

(3) Cultures from different sources have different characteristics but can be readily distinguished.

(4) Morphological and bacteriological characteristics demon-

strated in bouillon and agar-agar cultures differ according to virulence and degree of attenuation.

(5) The organism introduced into the stomach is pathogenic, provided corn is fed at the same time.

(6) The disease experimentally produced in the guinea pig was similar to that occurring in man. This was especially seen in the tardiness of the infection, the symptoms, and the organic lesions. The point of election of the organism in the guinea pig was the intestine. The intestinal changes were of a destructive, hemorrhagic character, accompanied by a general intoxication, whose effect was chiefly on the nervous system, the blood vessels, the red blood corpuscles, and secondarily on the liver and kidney.

Tizzoni's work was the most important ever done on the specific cause of pellagra linked with the deterioration of maize. It did not produce so much of a sensation as did the work of Lombroso, but his results were much more convincing. The reaction produced by the action of the blood serum of healed pellagrins on guinea pigs experimentally inoculated was, at least, very suggestive. But the whole question depends on the identity of the condition produced by the action of the strepto-bacillus. It seems more reasonable to suppose that the symptoms produced by this organism were more nearly pellagra than the symptoms produced by Lombroso. It becomes necessary to again consider the question, Can pellagra be produced in the lower animals? The most important work on this subject was done by Lavinder and Anderson in the laboratory of the United States Public Health and Marine Hospital Service. Their work was done on the rhesus monkey, using material from acute cases of pellagra. In all but one case of a number of experiments the results were negative. In this one case the results were not positive enough to justify any valuable conclusions; it was merely suggestive.

Being deeply impressed with the work of Tizzoni, I spent two years experimenting with the same organism. Through the courtesy of Professor Tizzoni I was able to secure a couple of preparations of his organism. It was not difficult to isolate the same organism here, both from the acute cases and from the

maize. After a careful study the only conclusion that seems justifiable is that the disease produced by the strepto-bacillus of pellagra (Tizzoni) was not pellagra. It was my experience in a large number of acute cases that the cultures remained sterile when clinically there was every reason to expect a growth and the reverse was occasionally the case. The finding of the organism was so uncertain that another source of its occurrence was sought. It seemed reasonable at one time to suspect that this organism was merely a skin contamination. The results in my laboratory were not sufficiently conclusive to be of any value and the work was abandoned, though I have seen falling of hair and emaciation in a guinea pig, and death, and the autopsy finding of a perforated bowel. All of the postulates of Koch were satisfied, but even the most important link in the chain was lacking — the establishment of the identity of this condition with pellagra in man.

Babes and Manicatide, Antonini, and Mariani, from experiments performed by them respectively, concluded that there existed in the blood of cured pellagrins a specific antitoxin against the poison of spoilt maize.

The toxico-infective theory was that there was formed in the body from spoilt corn certain toxic substances or endogenous toxins and that the disease was a sort of auto-intoxication or possibly an intestinal mycosis. Neusser thought that there was formed in corn a "receptive mother substance,"[1] due to the bacterium maidis which underwent in the intestinal tract a change and became toxic. De Giaxa[2] and Di Donna thought that the common colon bacillus became greatly modified by its contact with maize. It then became responsible for the disease.

In 1902 Ceni attributed the cause of pellagra to the aspergillus fumigatus and the aspergillus flavescens and developed a theory that an attack of pellagra at one season was due to a par-

[1] Neusser, E., "Untersuchungen über die Pellagra," *Wien. Med. Wochr.*, 1887. Also, Neusser, E., "Die Pellagra in Oesterreich und Rumaenia." This report was also read before the K. K. Arztliche Gesellschaft in Vienna, Jan., 1887.

[2] De Giaxa, "Pellagra," *Manuale d'igiene pubblica*, 1890–1892.

ticular fungus, while an attack at another season was due to the other. He found the aspergillary infection usually in the lungs, pleura, pia mater, pericardium, and mesenteric glands. The aspergillus fumigatus was the more pathologic and had its period of activity in the spring, while the aspergillus flavescens displayed its activity in the fall. He thought that maize was not an essential but that the moulds in question found it a much more suitable culture medium than any other grain, and when the growths occurred on maize their toxicity was increased.

Another notable contribution to the study of the etiology of pellagra was made by Neusser of Vienna, who was delegated by the Austrian government to report on pellagra in that empire and in Roumania. He began this report by the statement that maize was the cause of pellagra because the disease did not appear in any section until after the introduction of the American cereal. Some of his observations would tend to strengthen the claim of Sambon, which will later be referred to at length. Neusser did not believe in the theory of the insufficiency of maize because he failed to find pellagra in many countries where the people were very poor and the food was exclusively of maize, rice, or potatoes. The scourge was generally disseminated all over Roumania among well-nourished people who ate besides corn, meat, vegetables, and dairy products. In this his observations are in accord with our observations in North Carolina, as stated on a previous page. Neusser said that corn did not contain the pellagrinous substance or poison, but the mother substance (substantia mater), which in a normal condition of the digestive apparatus is digested or eliminated without any damage to the organism, but if the digestion is disturbed and the digestive secretions altered, there results abnormal fermentation processes, and then in such a medium this mother substance becomes a veritable poison. In this manner he explained the fact of the immunity of almost all domesticated animals to the supposed poison of maize; the comparative tolerance of children for the same poison; the fact that pellagra appears in so many different periods of life; and the fact that some tolerate bad polenta for a long life and finally in

old age succumb; and finally in some families with numbers of members oftentimes only one will be affected. He claimed that all of these facts argued against a pure toxic or intoxication theory. He came then to the conclusion that the disease was the product of two factors. One was to be found in the deterioration products of the corn and the other in the condition of the organism, hence he regarded pellagra as an auto-intoxication. The deleterious substance contained in the maize was regarded as a glucoside substance, which became active only in an abnormal state of the digestive tract. Alcohol was thought to play an important part by producing a gastroenteric catarrh and by a depressing effect on the organism. But the effect of alcohol generally was not considered; it was thought that the trouble lay in alcohol made of maize which had become deteriorated. All alcohol in Roumania is made from maize, according to Neusser. In his chemical study he found in damaged corn a substance which had the characteristics of an aldehyde and which he thought arose from the decomposition of more complicated substances as resins and glucosides. He also thought that it was possible for other cereals to contain pellagrous material. He concluded his report with the statement that the toxic principle owes its origin to substances which in themselves are not poisonous and which are probably developed through the action of the bacterium maidis. As a prophylactic recommendation to the Austrian government he offered the following:

(1) To cultivate only that variety of corn which matures quickly and thoroughly.

(2) To adopt, as Italy had already done, the drying apparatus for corn intended for food in order to prevent the development of the bacterium maidis.

(3) To establish according to the Mexican system stores for the preservation of maize which shall be under control of the government.

(4) To encourage the cultivation of other grains and also vegetable food.

(5) To improve the purity of portable waters.

(6) To establish colonies for the employment of pellagrins with suitable pursuits.

(7) To improve the sanitary conditions in that region between the sea and the Italian frontier.

In 1890 there appeared the report of Gaetano Strombio, Jr.,[1] on the sanitary aspects of the pellagra problem in Italy. It is a report of great exhaustiveness, going into the laws and provisions for the proper care of maize.

Raubitschek[2] applied the biologic, serologic, and anaphylactic deviation of the complement as well as other means to test the basis of the various theories of the etiology of pellagra. He decided that none of the theories were reasonable. He tried to show that pellagra and beri-beri were the result of the action of some toxin in maize and rice which must be sensitized by the chemical rays of the sunlight before any toxic action can be displayed. He found that animals fed corn and rice did not develop symptoms until exposed to the sunlight, when there soon appeared emaciation and paralytic symptoms which resulted in death after a period ranging from eight to twenty-one days. Animals removed from the sunlight early in the disease process promptly recovered, even though the diet remained unchanged. He concluded that pellagra was an alimentary poison, which required the addition of sunlight before it became active. Some of these experiments were performed with buckwheat. Animals so fed and kept in the dark developed no symptoms, but when exposed to sunlight the hair fell out and emaciation and paralysis resulted. This condition, which is known as fagopyrism, is strikingly similar to pellagra, especially in regard to the seasonal variations and the occurrence of the skin disturbances on the parts exposed to sunlight. He thought that the pellagra toxin developed in those parts of the skin exposed to sunlight "from the action of the chemical rays on the lipoid, alcoholic-soluble element in

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[1] Strombio, Gaetano, Jr., "La Pellagra I Pellagrologi e le Amministrazioni Pubbliche. Saggi di Storia e di Critica Sanitaria." Milano, 1890.

[2] Raubitschek, Editorial in *Jour. Am. Med. Assoc.*, LV, and quoted by Lavinder and Babcock in the translation of "La Pellagra," by A. Marie.

corn." There is still a large field for research in order to determine the toxicity of corn, and until more work of this nature is done there must remain a doubt in the minds of many regarding the nature of the poison which produces the various symptoms recorded in the lower animals. At this time it cannot be said that pellagra has ever been produced experimentally.

Black and Alsberg[1] state that the tests for the acidity of corn are very important and in a measure, at least, determine the noxiousness of the grain. It may be that this acidity about which they speak below may account for the symptoms produced in the lower animals without necessarily being connected with pellagra. They say:

"Much stress is laid in Italy upon the determination of toxicity. Schindler does not even mention it. It is performed as follows: A weighed quantity of meal is extracted at about body temperature with 90 per cent alcohol for twenty-four hours. It is then filtered and the alcoholic filtrate evaporated until the alcohol is removed. The residue is taken up in water at a temperature of 40° C., made up with warm water to a definite volume so that 0.5 c.c. corresponds to about 0.5 grams of the meal, and an amount equivalent to 0.5 grams of meal injected subcutaneously into a mouse. Large quantities of liquid are often injected, but this seems open to objection in so small an animal. The mouse is chosen because it is supposed to be the most sensitive to the poison. The symptoms are described as consisting of clonic spasms and localized contractures of the muscles, embarrassed respiration, gradual paralysis, collapse, and death. Sometimes opisthotonus ensues. On autopsy little is said to be noticeable except inflammation at the site of injection and hyperemia of the cord.

"A sample of corn which was toxic when injected in the dosage given above was never encountered in the present investi-

[1] "The Deterioration of Maize with Incidental Reference to Pellagra," by O. F. Black and C. L. Alsberg. U. S. Department of Agriculture, Bureau of Plant Industry. Bulletin No. 199.

gation. However, the procedure was varied from that of the Italians because of the following considerations: The extracts may be very acid. It is well known that herbivorous animals are very sensitive to acids which they are incapable of destroying in their metabolism. The symptoms of such an acid intoxication (acidosis) are, however, different from those described above. The behavior of mice toward acid intoxication is not known so far as a hasty search of the literature has shown. It is therefore conceivable that some of the toxic effects of the injection of corn extracts may merely have been acid effects. For these reasons the solutions injected were usually neutralized. Perhaps that is why toxic effects were not obtained. In this connection it is interesting to note that Gosio and Ferrati distinctly state that alkali neutralizes the poison, and in another place that culture fluid of the Penicillium cultures become less toxic as the culture grows older and their acidity diminishes."

It is very probable that this acid quality of maize has been responsible for the pathologic effect produced in the laboratory animals after the feeding of corn, as previously described. As mentioned in the preceding chapter, the most important work yet done was that of Lavinder and Anderson in their study of the question of the transmissibility to the lower animals. The animal used by them was the rhesus monkey, but the results did not strengthen their belief in this possibility. It is hardly fair to accept any of the experimental work done on the lower animals because of this defect. Some other means must be found to establish the identity of these various conditions with pellagra before there can be any value in the conclusions. It does not seem to be a difficult matter to find causes for the disease conditions in the laboratory animals other than the possibility of pellagra. There are many forms of grain poisoning besides ergotism, and granting for the sake of argument that bad maize causes pellagra, it is probable that it also causes other forms of poisoning. Thus, it might be worth the time of some investigator to prove that the causes of death in fowl and cattle as well

as laboratory animals can be explained without incriminating pellagra.

The most startling theory of the etiology of pellagra was made by Professor Louis W. Sambon of the London School of Tropical Medicine before the British Medical Association in 1905 at the Leicester meeting. At this time he stated that he believed pellagra to be an insect-borne parasitic disease and that the specific parasite might be a protozoal organism. In 1910, at a meeting of the Pellagra Investigating Committee, he developed this idea by suggesting that the insect might be a Simulium. This hypothesis was founded on topographical and epidemiological facts. In 1900 and 1903 he visited some of the pellagra-affected districts of northern Italy where his first observations were made. This work is of so great importance and conforms so closely to the actual situation in North Carolina that it will be referred to here at great length. Sambon's report [1] brought forth a great torrent of objection and even of abuse. In this country many who had no right to any opinion denounced it as a hoax, and one elementary student of the disease went so far as to diagnose the condition of the eminent authority on tropical diseases as hysteria. But the earnest endorsement of such a student as Sir Patrick Manson more than over-balanced the opinions of these lesser lights. No theory has yet been advanced which so well fits into the real facts. In this theory it is at once appreciated that the author of it does not make the disease fit the theory as do the zeists, but the theory is the result of the most careful observation made in a scientific way and without bias.

He said in the beginning of his report: "The recent investigation carried out on behalf of this committee substantiates my suggestions, and, in my opinion, demonstrates the reliability of topographical and epidemiological data when correctly interpreted. In 1903, availing myself of similar data, I was able to infer that sleeping sickness is a tsetse-borne disease, and to indicate the very species of the carrier — *Glossina palpalis* — conclusions

[1] Sambon, L. W., "Progress Report on the Investigation of Pellagra." *Journal of Tropical Medicine and Hygiene*, 1910.

which subsequent investigations in Africa have fully established." His investigations were made in Italy in the provinces of Milan, Bergamo, Brescia, Padua, Rome, and Perugia.

In this report he took up the various theories and considered them in a systemic manner, thus:

The present theories of the etiology of pellagra now in vogue in Italy are as follows:

Fig. 2. — Peculiar Bodies Found in Nuclear Material from Cerebro-spinal Fluid, in Smears from the Sensorio-motor Cortex and from a Blood Clot Lying in Contact with and Posterior to the Lower Cervical and Upper Dorsal Regions of the Spinal Cord. (Reproduced by courtesy of Professor Sambon. *London Jour. of Trop. Med. & Hygiene*, Dec. 15, 1911.)

(1) Insufficiency of nutriment, owing to poverty, inappropriate food (maize), and lack of wine.

(2) Toxicity of maize, especially when used exclusively as an article of diet.

(*a*) Owing to specific toxins normal to this cereal, even when of good quality and perfectly sound.

(*b*) Owing to toxic substances produced at spring time, during the process of germination.

(*c*) Owing to toxic substances resulting from the action of *Bacillus coli* on sound maize, within the alimentary canal, after ingestion.

(*d*) Owing to toxic substances elaborated during the decomposition of maize.

(I) By the common blue mould, *Penicillium glaucum.*

(II) By certain particular strains of *P. glaucum.*

(III) By several kinds of fungi and bacteria.

(3) Parasitism of certain organisms ingested with either sound or deteriorated maize.

(*a*) Certain fungi: *Aspergillus fumigatus* and *A. flavescens.*

(*b*) *Strepto-bacillus pellagrae,* an organism which Professor Tizzoni claims to have isolated from the blood, cerebro-spinal fluid, tissues, and feces of pellagrins, as well as from damaged maize.

(4) Parasitism of a nematode worm, belonging to the family *Filariidae,* which Professor Alessandrini claims to have found in the skin of pellagrins and in the drinking water of affected districts.

All but this last mentioned are different phases only of the maize theory.

Sambon says the relationship of cause and effect between maize and pellagra is based on the following assumptions:

(1) The disease appeared for the first time in Europe soon after the introduction of maize from America.

(2) It followed everywhere the extension of maize cultivation, and increased *pari passu* with the more general adoption of the new cereal as an article of food.

(3) It occurred only in places in which maize is either grown or imported, and exclusively in people who use it as an article of food.

It is stated that the maize theory is supported by the belief that the disease has been diminished by the adoption of preventive measures. These measures are:

(1) The inspection of maize, and seizure of all unsound grain and its products.

(2) The exchange of deteriorated maize for good maize.

(3) The providing of drying apparatus for damp maize.

(4) The providing of suitable bakehouses in rural districts for the proper baking of maize bread.

(5) The abolition of late varieties of maize which do not ripen properly.

(6) The compulsory notification of all cases of pellagra.

(7) The obligation, in all affected districts, upon the municipal authorities to supply free meals to all their pellagrins twice every year for periods of not less than forty days.

(8) The institution of special retreats, "pellagrosari," for the housing, feeding, and treatment of the more advanced cases.

(9) The dispensation of free salt to all pellagrins and their families.

The following facts were thought by Sambon to argue against the maize theory:

(1) There is no foundation whatever for the belief that pellagra broke out in Europe soon after the introduction of maize from America.

(2) The topographical distribution of pellagra does not coincide either with the distribution of the maize cultivation or with that of maize consumption.

(3) The disease occurs frequently in persons who have seldom or never partaken of maize as an article of food.

(4) All preventive measures based on the maize theory have failed.

(5) The characteristic skin eruption and other symptoms of the disease may recur each spring for several successive years in patients who are far removed from the endemic districts and who abstain from maize.

Sambon thought that maize was introduced into Europe from South America by the Spaniards soon after the discovery of America. The proofs that this grain was introduced from Asia at a much earlier date are not considered sufficient to establish the claim. He further mentioned that he found the names "melega," "melica," and "formentone" used to designate maize as early as the middle of the sixteenth century. Savonarola in 1554 stated that bread made of "melega" was less nourishing than any other kind and very indigestible. There were many other references to writings of the sixteenth century which proved

that maize was an article of food at that time, though it had not come into such general use as it did later. It was used by the peasantry chiefly in times of scarcity and found its use chiefly as a food for fowls and other animals.

Fig. 3. — Professor L. W. Sambon Holding a Three-year-old Pellagrin.

It must be admitted then that if Casal's work indicated the appearance of a new disease in Europe it did not accompany the introduction of maize into the same territory, for we have seen that this grain was used as a food for a century and a half and in some instances two centuries before the date of the earliest record of pellagra. There is no way in which these two events can be connected, for any one who has read Casal's work will be

at once impressed with the important fact that in 1735 he had been observing the disease for many years and he never claimed priority in recognition or in the naming of the scourge. One would infer that in his time there was as much disagreement regarding the nature of the disease as there is to-day. Maize has been used in the United States as far back as our records go, and in Peru there are many evidences that it was an article of food many centuries ago, but with as much certainty we can say that pellagra has existed in this country only for a comparatively short period, even if we accept many unproved statements of its earlier appearance which are not recorded in the literature. As stated in the preceding chapter, the old writers on natural history of this country did not mention pellagra or anything akin to it, though the same writers did accurately describe uncinariasis.

He then shows many evidences of the fact that pellagra does not confine its activities to those who have eaten maize. The disease is shown to occur in countries where it is neither grown nor eaten. Such instances were found in his experience in Spain and France and in my own experience in this country. At a meeting of the Catalonian Academy of Medicine, Casana stated that the sad boast of the greater prevalence of pellagra belonged to those provinces in which the use and cultivation of maize were unknown. We read further in this exhaustive report many instances, even in Italy, of the fallacy of the maize theory. It would seem that one authentic case in which it could be shown conclusively that maize was never eaten would be enough to bring about a renunciation of the theory, but such has not been the case. I have selected only a few examples from Sambon's long list to add to my own previously mentioned cases. Doctor Conti, chief medical officer of the Province of Ravenna, said that pellagra was not confined to the small mountainous region where maize is eaten, but also in the district of Lugo where it is not eaten. In 1903, Garbini described five typical cases of pellagra under the name pseudo-pellagra because the patients were lunatics who had never eaten maize. This is a very significant utterance and deserves a careful consideration in this connection. He said:

"Although all the symptoms indicate pellagra, in view of our present knowledge concerning its etiological factors we cannot consider our patients to be pellagrins. The entire absence of the etiological element of pellagra, as also the fact that they are not the progeny of pellagrins, dissuade us from forming such a diagnosis and confirms us in the belief that the dread disease does not occur in Sicily. It is a well-known fact that in this island maize is neither grown nor imported from abroad for local consumption, since it is neither eaten in the form of polenta nor in that of bread. Only very exceptionally it is eaten grilled on a charcoal fire. The Sicilians, says Tonini, may be extremely poor, indeed, they may live solely on the parings of prickly pears, but they will never eat maize, which is totally unknown to the majority of them. It might be suggested that what is not done by all might be done by a few for special reasons. This, however, is not admissible in the case of our patients, because for several years they had lived in the asylum, and through information obtained both from their respective families and themselves we learnt in the most positive manner that they had never eaten maize.

"Nor can the opponents of the maize theory, if there be still any, avail themselves of these five cases of mine to breathe new life into the inanition theory, because it will suffice that I point out that our patients had already been a long time in the asylum where the food has always been plentiful and of good quality, and that even before admission, though poor, had never suffered from starvation. On the other hand, since we are unable to ascribe the erythema to the use of alcohol on account of the time they had been in the asylum and because they had always been abstemious before admission, we are led to the conclusion that our patients are suffering from that form of chronic dermatitis which A. Brianchi, among others, believed to be due to the sun's rays, and which, indeed, is called pellagra or pseudo-pellagra of the insane."

Professor Tambourini showed to Sambon and Lavinder a case in his ward which came from the mountain village, Rocca Priora,

in the Roman territory. This was the first case of pellagra from this place and maize could not be connected with its origin nor was there a history of alcohol or syphilis. The erythema had appeared two years previously and there was mental confusion, paresis, and rigidity of the trunk and limbs. He was a field laborer, and while his family ate polenta two or three times a week, he would never partake of it, always eating wheat bread; but the other members of his household remained well. It was a typical case of pellagra and the diagnosis was concurred in by both Lavinder and Sambon, who had seen many cases of the disease. There were many more examples just as convincing as this one.

Sambon quotes the following paragraphs from an address of Prof. G. Sanarelli, under-secretary of state for agriculture, at the 1909 Pellagra Congress:

"The beneficial results derived from the application of the law of 1902 became evident so soon that already in 1905, less than three years after its passing, the pellagrins within the kingdom were reduced to barely 55,000, showing a decrease of over 17,000 in the last six years.

"Until we have a new pellagrin census to confirm the increasingly progressive reduction of this social sore, which, fortunately for our country, is gradually healing, we must from this very moment draw the most auspicious omens from the continuous and marked decline of the death rate due to pellagra within the last few years.

"Indeed, whereas in the three years, 1887–89, the victims of pellagra throughout the whole kingdom were 10,284, in the next three years, 1900–02, they fell to 9,218; in the three years following, 1903–05, they further declined to 7,367; and in the last three years, 1906–1908, they have fallen to 4,649 only.

"But there is something still more comforting. Whereas in 1907, 4,950 new cases were notified, last year only 2,824 were reported. Whereas before the application of the present law, the yearly pellagra mortality constantly reached or even exceeded

the figure of 3,000, immediately after the year 1902 the number of deaths only just exceeded 2,000, in 1907 the deaths were 1,635, and last year they were reduced to about 1,000.

"Now, if on the basis of the last censuses of 1889 and 1905 we can reckon that about 24,000 notified pellagrins corresponded to every thousand deaths from pellagra, we are bound to conclude that at present, within the whole kingdom, these unhappy beings do not exceed the number of 25,000.

"Therefore, the prophylactic and curative work carried out within the last three years has further reduced the number of pellagrins by more than 50 per cent.

"And this is a sure indication that the combined action of both the Government and the local bodies have attained decisively positive and greatly beneficial results."

He further stated that if the law had been more vigorously enforced in all the forty-four affected provinces, the disease would have been wiped out. Sambon attempted to show that the law of 1902 did nothing at all in the direction claimed by Sanarelli. He said that the decline had already begun before the enactment of this law and that the law of 1902 did not go into effect until three years later, and then only for some of its least important provisions. He quotes an earlier statement of Sanarelli that went to show that notwithstanding the various reform movements there was no reduction in the number of cases. He then showed the obvious defects in all the prophylactic measures which the Italian Government had adopted. The reporting of cases, which by this law was compulsory, was absolutely farcical, as was the rule prohibiting the cultivation of the late varieties of maize, — that is, those varieties maturing late in the season, as forty-day and fifty-day corn. Until there is a more rigid supervision on the part of the Government it would seem hardly fair to draw deductions from the results. Certainly the decrease in pellagra in Italy cannot be attributed to these laws which have never been enforced.

Sambon's idea that pellagra was a parasitic, insect-borne disease transmitted by an insect of a blood-sucking type had its inception

before he left London on his tour of investigation. The reasons for such a belief were as follows:

(1) (*a*) The characteristic eruption and other symptoms of the disease may recur each spring for a number of years, notwithstanding the removal of patients from the endemic districts and the strict elimination of maize from their diet. This peculiar periodicity of symptoms can be explained only by the agency of a parasitic organism presenting definite alternating periods of latency and activity. Analogous periodicities are met with in other parasitic diseases — as, for example, in tertian fever, in which the periods of activity of the parasite (*Plasmodium vivax*) recur each spring in correlation with the activity period of its anophelic definitive host. No toxic substance could account for it.

(*b*) It presents peculiarities of distribution and seasonal incidence as in all parasitic diseases.

(*c*) Its symptoms, course, duration, and morbid lesions are analogous to those of other parasitic diseases.

(2) It is an insect-borne disease because:

(*a*) It is not directly contagious.

(*b*) Neither food nor drinking water can account for its peculiar epidemiology.

(*c*) It is limited to certain rural districts only, towns and villages almost invariably escaping.

(*d*) It presents a definite and peculiar seasonal incidence — viz., spring and autumn.

(*e*) It is practically restricted to only one class of people — viz., the field laborer, owing to greater exposure to infection.

(3) It is conveyed by a Simulium because:

(*a*) Simulium, so far as we know, appears to affect the same topographical conditions as pellagra.

(*b*) In its imago stage it seems to present the same seasonal incidence.

(*c*) It is found only in rural districts and, as a rule, does not enter towns, villages, or houses.

(*d*) It explains most admirably the peculiar limitation of the

disease to agricultural laborers, a limitation which nothing else can explain in a satisfactory manner.

(*e*) It has a wide geographical distribution, which seems to cover that of pellagra, although certainly exceeding it, in the same way that the distributional area of the anopheles exceeds that of malaria, and the range of *Stegomyia calopus* that of yellow fever.

(*f*) It is known to cause severe epizoötics in Europe and America.

(*g*) Other similarly minute blood-sucking diptera such as *Phlebotomus papatassi* and *Dilophus febrilis* are strongly suspected of being propagators of human diseases.

Sambon found in Italy a peculiar attitude on the part of the medical profession, even those in the universities, towards pellagra. There were many errors of diagnosis; such diseases as ankylostomiasis, dysentery, syphilis, and vitiligo being confused with it. In some instances the diagnosis was made on the gait, in others on the vertigo and debility. The value of the symmetrical erythema as a pathognomonic sign was not appreciated, and its absence was not regarded as very important in arriving at the diagnosis. It was considered not an unusual thing for the skin lesion to be absent throughout the whole course of the disease. On the other hand a symmetrical erythema commonly observed was called by them "ethyl erythema," because it was attributed to alcohol. Sambon found that this so-called alcoholic affection was really pellagra occurring in the alcoholic individual. He also found that it was not an uncommon thing for the true pellagrous erythema to be overlooked by the physician. He concluded that the erythema was the earliest, most distinctive, and essential manifestation of the disease. This has been my experience, and I have never seen a case of pellagra in which the erythema was absent throughout the whole course of the malady. As stated on a previous page, I did not find, as did Sambon, that it was limited to the agricultural population. From his report we see at once that this observer had a very thorough knowledge of the nature of the disease and, in fact, his description is one

of the best to be found in the English language. One could hardly view lightly any statement this man would make. He said:

"After surveying several districts I became more or less familiar with the nature of the pellagra haunts, so much so that in Umbria, on visiting new districts, which could be viewed from the commanding height of their inhabited center, usually perched on a high hill, I ventured to tell the local health officers whence I thought their pellagrins came from, and my guess was invariably right.

"Both in northern and central Italy I found that the pellagra stations are, as a rule, in the narrower valleys of hilly and wooded country, trenched by swift-running streams infested with Simulium. This is the reason why pellagra is so common among the foothills of the Alps and Apennines, but the disease also spreads out into the plains, following the streams as far as the fly will reach, alternately extending and restricting its domain with the flows and ebbs of Simulium life.

"That pellagra is especially prevalent about the lower slopes of mountainous regions was known long ago. Indeed, Pujati (about 1740) gave it the name 'Alpine scurvy,' and Sartago (1791) proposed to call it 'mountain scurvy,' and Odoardi (1776) described it as a disease peculiar to the mountains and valleys of Belluno, expressing the belief that it would probably also be found in other mountainous countries. Strombio (1794) pointed out that it lurked among the hills of Brianza. And Cerri (1807) stated that pellagra is essentially a disease of the hills and lower mountains.

"In all its European centers, whether in Italy, Portugal, Spain, France, Austria, Hungary, Croatia, Dalmatia, Bosnia, Servia, Bulgaria, Turkey, Greece, Roumania, Bessarabia, Kherson or Poland we find pellagra stationed at the base of the mountain ranges, along the streams which flow out of the mountain valleys into the subjacent plains.

"So far as I know, prior to my papers on the etiology of pellagra, no causal connection was ever suspected by any one be-

tween pellagra and streams of running water, notwithstanding that numerous authors had mentioned the special prevalence of the disease along the banks of certain water courses. Odoardi (1776) pointed out that pellagra is very prevalent along the left bank of the Piave; Strombio (1794) noticed that it is common 'among those who dwell along the River Olona'; Pagani (1806) stated that in Friuli the disease extends along the banks of the Tagliamento from S. Daniele to Valvasone; Arrigoni Degli Oddi (1883) refers to the fact that near Padua the disease has been observed, as a rule, along the course of the canals; Esposito (1902) reports a case from southern Italy, at S. Stefano, a village placed on the slope of a hill skirted by a rushing torrent, and not far from Nocera Inferiore, where other cases have been observed. Even in other countries the disease has been noticed to prevail along the banks of rivers and brooks. Thus, in Hungary, Doctor Takacs (1889) observed it constantly along the banks of the River Szamos in the district called Szilagysag. Quite recently (May, 1910) Professor Alessandrini has confirmed my statement of a connection between stream and pellagra, but he repudiates the hypothesis of an insect carrier, and ascribes the disease to a nematode worm of undetermined genus, which he says he has found in the streams and is taken up in drinking the water thereof. His observations were carried out in Umbria, and more especially in the Districts of Gualdo, Tadino, and Assisi. 'In the former district,' he says, 'I was able to notice that the distribution of pellagra is typical and sharply limited by the course of two streams, the Rasina and the Sciola. These, together with the railway line, Roma-Ancona, divide the territory into two districts, — one mountainous, consisting of the high Apennine Mountains, the other all hills. Whilst in the former there are no pellagrins, the latter, in all its fractions (Morano, Cova dell' Occo, Grello, Pastina, Badia, Pieve, San Pellegrino, Piaggie, Poggio Ercolano) is full of them, so much so that all the pellagrins of the District of Gualdo Tadino (254 people: 192 women, 62 men) belong to these fractions. The same may be said to be the case in Assisi, where the fractions most affected are those of the plain and hills.'

"The first pellagra district I had the opportunity of visiting this spring was that of Trescore Balneario, in the Province of Bergamo, where I went with Professor Balp, Drs. Siler, Perico, Baldini, and Mr. Amoruso. There, the very first pellagrins I was taken to see dwelt along the Tadone, a swift-running stream which flows into the River Cherio. On the slabs and boulders which form the bed of the Tadone we found numerous larvæ and pupæ of at least three different species of Simulium. Two of these, of which we reared adult specimens, were sent to Mr. Austen for determination and were found to be *Simulium pubescens* Macq., and *S. ornatum* var. *fasciatum* Mg.

"After that first observation, wherever I found endemic pellagra there also I found both stream and Simulium.

"Professor Balp, to whom I had explained my theory, stated that his mind was quite open with regard to the etiology of pellagra, but that he knew of numerous cases of the disease in mountain districts far above any stream. I said those were the very districts I should like to visit so that I might at once dismiss my theory if it failed to explain satisfactorily the distribution of the malady. Accordingly, Professor Balp took me to Clusone, a small historical town on the slope of a mountain, at 648 meters above sea-level. To get to Clusone from Bergamo, one travels by train along the glorious valley of the Serio until one reaches a place called Ponte della Selva, then the road winds up the mountain through a forest of stately pines. Whilst driving up, I said to Professor Balp and Doctor Perico that, judging from the nature of the place, I should not expect to find any pellagra at Clusone. But Professor Balp took out of his pocket-book the official list and said there were no less than eighty-three cases notified. I have already stated that when we got to Clusone we only found a single imported case of many years' standing. At Clusone we partook of luncheon, and when we were served the inevitable 'polenta' some one jocosely asked the local physician whether it could be eaten without fear of contracting pellagra. I then ventured to say that the pellagra we had not seen at Clusone would probably be found down by the Serio at Ponte

della Selva. Doctor Perico offered to go with me, and we started down the road that leads to Ponte Briolta, whilst the others followed DeVille, who went into the pine forest to shoot woodcock. Doctor Perico and I reached the Serio at a place called Piario. The few houses which form the hamlet seemed deserted, all the good people of Piario were out in the fields with the exception of an old goitrous female of facetious humor who could give us no information. However, in the following stream, we met a young woman carrying a child in her arms, and we found that the child had a typical pellagrous rash on hands and face, though the mother was quite unaware of the nature of the eruption, which she believed to be the redness of severe sunburn. This woman told us of a carpenter of Piario who was known to be a confirmed pellagrin, but we were unable to see him because, at the time, he was a long way off mending a roof.

"The check at Clusone did not disconcert Professor Balp; he owned that, with regard to that place, he had relied on local information, but he insisted that there were other places higher up in the mountains, such as Castione della Presolana, at 870 meters above sea-level, where he had himself not only seen but even photographed numerous pellagrins. Therefore, on another day, we made an excursion to Castione, at the foot of the snow-clad Presolana, and there we certainly did find many cases of pellagra, but as already stated, those we examined proved to be imported cases. However, Castione has its stream of rushing water, the Torrent Borzo, in which Professor Balp was the first to find a few Simulium larvæ.

"At Padua, Professor Stefani and Doctor Randi, to whom I also explained my views on the etiology of pellagra, said they doubted whether my theory could hold good in their province, because there were many cases of the disease in the neighborhood of the town of Padua, but no torrents or swift-running streams, and that the disease was prevalent among the Euganean Hills, a volcanic group noted for the scarcity of water.

"The provincial medical officer, Doctor Randi, and Professor Stefani drove Doctor Siler, Mr. Amoruso, and myself to Chiesa-

nuova, where the local health officer, Doctor Carrer, showed us the locanda sanitaria, and then took us around to see the family Pavinato, with five pellagrin children, already mentioned, and another case of a child aged seven, belonging to a family of well-to-do farmers. As we drove along the dusty road which runs in a straight, staring white line along the perfectly flat country, and saw nothing but pools and ditches of stagnant water almost covered with Lemna or Spirogyra, Doctor Siler began to chaff me about my theory. Where was I going to find the howling torrent, the flying stream, and the aerated-water-loving midge? Certainly, it was obvious that there could be no roaring mountain torrent in the level Paduan plain, but, perhaps, the pellagra cases notified in that district might prove to be imported cases, or there might be rapidly flowing irrigation canals that we had not yet seen, or, again, Simulium in the choice of its habitat might not always adhere quite strictly to the rules set out in the entomologist's text-book. At the locanda sanitaria of Chiesanuova the commensals we found gathered there were like the commensals of all locande sanitarie, a motley assemblage of poor, sickly creatures, several of whom presented the signs of a pellagra infection of long standing, probably contracted many miles away. I did not trouble about them. With regard to the Pavinato children I was able to ascertain that they had contracted the disease many years ago, probably elsewhere. It would have been apparently reasonable, therefore, to dismiss this case as one of hereditary transmission, but I am very doubtful about this mode of transmission, and I chose to look upon it as a proof that pellagra is endemic, or at any rate it is capable of transmission in the District of Chiesanuova.

"The day following I had arranged to meet Doctors Lavinder and Blue, who were coming from Milan to see some typical cases of Italian pellagra; I, therefore, instructed Mr. Amoruso to return very early next morning to Chiesanuova, examine the water courses of the district, whatever their nature, and endeavor to find me a test-tube full of Simulium larvæ by noon, when I expected to reach Chiesanuova with the American colleagues. Pellagra appeared to be endemic in the district; if this were so, then to

the best of my belief Simulium must be present; to him the task of finding it. At the appointed time, on approaching Chiesanuova, I saw Amoruso in the distance waving a test-tube, and I knew that he had been successful. He did not find many larvæ, but he discovered a number of pupæ and empty pupæ-cases in sluggish and almost stagnant water courses. The peasants who watched him collect the cocoons of the tiny aquatic silkworm told Mr. Amoruso that in early spring all the water courses run far more swiftly.

"In all districts comprising both low, flat, or hilly, well-watered areas, and more or less massive mountainous areas, I invariably found pellagra to prevail in the former, and to be absent in the latter."

Thus, at considerable length he details case after case to show that the two conditions, pellagra and swiftly flowing streams infested with the Simulium, went hand in hand. Where he found the Simulium he always found pellagra and the converse was equally true. He points out that the epidemiological picture is much like that of trypanosomiasis, Rocky Mountain fever, and malaria as well as other diseases transmitted by insects and having very definite habitats. Out of the endemic centers the sporadic cases were found to be in those who were in the habit of frequenting infected districts. He further shows that in the endemic centers the disease attacks all ages and sexes and even whole families. He mentions the case of two peasants who had lived by the Torrent Nestore, but were compelled to abandon it because of the pellagra. As soon as they took up their residence elsewhere the disease disappeared. Cases are cited where pellagrous parents having pellagrous children after leaving the "fly district" would have healthy non-pellagrous children born to them.

Sambon emphasizes the definite areas of endemicity and states that these areas do not change from year to year. It is too soon to say with any degree of accuracy that this statement would hold true in the infected portions of the United States. Certainly, I

have seen a number of cases in one neighborhood and I have also seen six cases in one house. One of my patients was the wife of a man who had died during the year previous of pellagra. It cannot be said that these areas occur always out of the cities and towns. Such was Sambon's experience, as well as the experience of practically all who have written on the subject. In North Carolina we see many cases in such cities as Durham, and we often hear of cases occurring in Atlanta. This fact does not weaken Sambon's theory in my opinion because of the fact that many, if not all, of the victims can be shown to have visited the country at some more or less remote period. The possibility of such an inaccuracy and such a point against Sambon's theory recalls to my mind the beautiful English Garden in Munich with the "Iser rolling rapidly" through it, and I wonder if, in the event of pellagra ever occurring in this fascinating Bavarian city, it would be a point against the Simulium theory. I recall the case of a miller who owned a mill for the grinding of corn into meal by water power. He developed pellagra, and the idea was that the disease owed its origin to the habit of eating raw the grains of corn during his work. It would be equally as fair and possibly more so to attribute the trouble to the Simulium-infested stream.

It is a notable fact that such eminent pellagrologers as Babes of Roumania, whose work has previously been referred to, have left the maize theory to accept this of Sambon. Likewise, this view is upheld by Sir Patrick Manson in the last edition of his book and also by Castellani and Chalmers in their writing on tropical diseases.

For my own part I feel confident that we are dealing with a parasitic disease, though I am not satisfied that the Simulium is the particular intermediate host in the transmission. Much more must be done before even Sambon himself would be willing to quietly accept this view. In the United States we are taught by no less an authority than L. O. Howard that this theory is not possible, for the reason that the Simulium habitat does not conform to the endemic centers of the disease. However this may

be, I was unable to secure any knowledge from Washington that helped to solve the question, so I proceeded to investigate for myself. I soon learned that the buffalo-fly was well known to all cattle people, and I also found that there was one specimen in the North Carolina Museum at Raleigh. Surely this one fly did not arise spontaneously so many miles away from the habitat in New York State, which is the only definite habitat I have been able to acquire any knowledge of from authorities. I would be unwilling to accept the information obtained from the country people regarding this fly until it is further investigated. It is a fact that the habitat of pellagra in North Carolina is not along the sea coast where the streams are tidal and more or less sluggish, but in the Piedmont section where the towns are situated on rapidly flowing streams which are made use of in the various manufacturing industries for which this state is famous. In the high mountains I have been unable to find the disease except sporadically, and in the hospitals in Asheville only a small number of cases have been collected from the adjoining mountainous counties. In 1907 we saw a large number of cases in Wilmington, but recently in that city the disease has become very rare and all of my cases for the past three years have come from the interior counties. On reviewing the earlier cases in the light of Sambon's hypothesis, that is, from a geographical standpoint, I was impressed with the fact that a large number of those people, who had been affected with pellagra in this coast city, were newcomers. I hope to be able to prove that the others were exposed to infection during visits in the hill country. There are isolated cases where the disease has occurred on the very beach of the Atlantic Ocean, but in these cases I was able to find rapidly flowing brooks, which had a considerable fall in the last few hundred yards of their course before entering the sounds. It is not unlikely that the Simulium will be found to have a suitable abiding place even this near the ocean. It has often been a problem to us why Onslow County in this same state was never infested with pellagra, as it has a relatively large number of poor whites and hookworm disease is very prevalent. The surrounding coun-

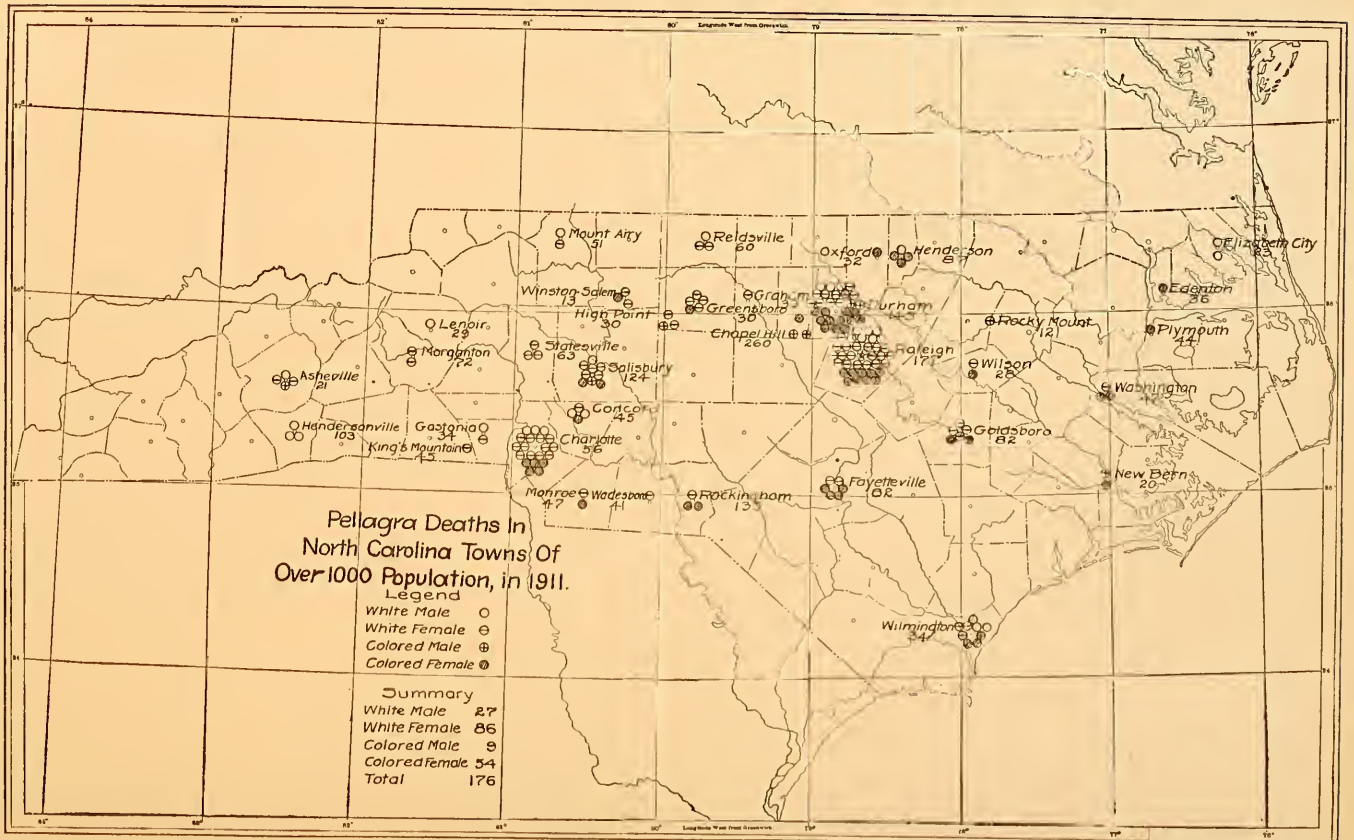

FIG. 4. — MAP SHOWING PELLAGRA DEATHS IN NORTH CAROLINA TOWNS. (Prepared for the author by the North Carolina Board of Health.)

ties have suffered from pellagra much more. In fact, until quite recently no cases were discovered there, in spite of the fact that it is famous for its excellent medical profession, and every physician in the county was familiar with the disease. This county lies on the Atlantic and is very low, with only tidal water, and no rapidly running streams. It is a notable fact that pellagra is more prevalent in those sections where there are to be found water mills. Can this be due to the fact that this water is the favorable breeding-place for the host?

The work of S. J. Hunter, professor of entomology in the University of Kansas, deserves especial mention and commendation.[1] The first authentic cases of pellagra occurred in Kansas in July, 1911, and the State Board of Health, through its secretary, who was Dean Crumbine of the University of Kansas, determined to have the sand-fly theory investigated. Consequently on August 1 a survey of the streams in the vicinity of the cases was made. As the streams were muddy and high from recent rains the adult fly was sought first. The writer had had previously in the Mississippi valley between Keokuk and Fort Madison, Iowa, an opportunity to study the workings of the adult female, which is the biting sex, on horses, especially colts. The fly is so vicious that after warm rains it attacks the stock in such a manner as to actually denude the ears and throats and expose patches of raw flesh. On the date mentioned numerous specimens were collected from the ear of a brood mare and, when the streams had fallen, abundant larvæ and pupæ were found. Within four hundred yards of the home of the pellagrins was a small stream. Attached to the tree roots in this stream was found a large colony. The root produced a sufficient ripple in the water for the safe development of the eggs. The only species of the sand-fly found in Kansas was the *Simulium vittatum*. So far, the *Simulium reptans* has not been found on this continent, except in Greenland. Hunter's experiments consisted in allowing the *Simulium vittatum* to bite one of the pellagrins. Until October 12 he noted that

[1] Hunter, S. J., "The Sand-fly and Pellagra," *Jour. Am. Med. Assoc.*, LVIII, pp. 547 and 548.

the fly would not bite, but from that date on they bit freely, drawing blood. By November 8 the male monkey which was bitten in turn by the fly which had previously bitten the pellagrin showed signs of inactivity and rapidly became decidedly ill, "crouched on the floor of the cage and was both unwilling and unable to ascend to his perch. He remained ill all day, getting worse, till late in the afternoon he became flaccid and motionless save for a high rate of respiration, ranging from 45 to 60 per minute. His temperature was 103.6° F., a little above normal. He appeared about the same the next morning, but improved a little during the day and continued the same until November 12, refusing all food, but drinking water freely." This work is still being carried out and one would be justified in expecting splendid returns from it.

Grimm of Savannah has made an interesting study of the epidemiology of pellagra from the standpoint of topography.[1] He found that in his series of sixteen cases studied that all of them lived within five hundred yards of a running stream; the majority lived within two hundred and fifty yards, and some actually on the very banks. These people lived in the valleys for economic reasons and consequently the streams were quite rapid. No work was done to determine the presence or absence of the *Simulium* group of biting flies.

The cotton-seed products theory of Mizell was brought forward in 1911.[2] There hardly seems any occasion to discuss it at any length. It is not probable that the Spanish, French, or Italian peasantry nearly two hundred years ago were exposed to this danger. As to the adulteration of olive oil with cotton-seed oil it will be seen that more peanut oil is introduced into France each year than cotton-seed oil. Peanut oil is much more often used to adulterate olive oil than the cotton-seed oil. It should be remembered that in Greece pellagra has never made any great inroads, according to the literature, but it is a well-known fact

[1] Grimm, R. M., "Pellagra: A Study in its Epidemiology." *Lancet-Clinic*, March 2, 1912.

[2] Mizell, in *The Journal-Record of Medicine of Atlanta*, 1911.

that these people eat olive oil on Wednesdays and Fridays, according to a rule of the Greek church; during Advent and during Lent this oil takes the place of meat. There is no evidence in the United States that the consumption of cotton-seed oil has been associated with the appearance of pellagra. I heartily agree with the wise utterance of Zeller when he strikes a note of warning against the condemnation of valuable food stuffs. If the use of maize and fat is taken away from the poor whites of the South what will be left for them to subsist on? In my own practice among these poor, unfortunate victims of pellagra I propose to add to their diet as much peanut oil, cotton-seed oil, and olive oil as their deranged digestive apparatus will stand. I have been accustomed to advise the use of cotton-seed oil among my tubercular patients when they were too poor to buy olive oil, and I have yet to note any ill results from it. It has been contended that cotton-seed would kill hogs after one year's feeding and that the trouble lay in some toxic substance contained in the seed. It has been demonstrated by Mr. W. E. Worth of Wilmington, North Carolina, who is a large cotton-seed manufacturer, that hogs can be successfully fed cotton-seed without any result except the very best fattening returns. In certain experiments performed by him it was shown that the supposed cause of death is not toxicity, but the fact that the lint on the cotton-seeds is not digested but forms tough masses in the intestinal tract, which finally results in complete obstruction and death. When delinted seed was used there was no such ill result and the animals remained in the very best condition.

CHAPTER III

GENERAL CHARACTERISTICS OF THE DISEASE

Pellagra is an endemic disease of unknown cause, occurring usually in temperate and subtropical countries, characterized by symmetrical skin lesions, chiefly of the exposed portions of the body, by gastrointestinal disturbances, and by changes in the nervous system. It is generally chronic in nature and terminates in recovery, insanity, or death.

The disease attacks all ages and seems to be peculiarly free from any tendency to select a particular period of life. My youngest patient was 22 months and the oldest 75 years with all ages between equally affected, except in infancy and childhood when the occurrence is said by most observers to be unusual. In the Peoria State Hospital [1] the following was the distribution of cases:

From	20 to 29	years	4 cases
"	30 to 39	"	18 cases
"	40 to 49	"	28 cases
"	50 to 59	"	29 cases
"	60 to 69	"	16 cases
"	70 to 79	"	3 cases
"	80 to 89	"	2 cases

Merk's table is of greater value for the reason that the above table was made from the inmates of an insane institution where there were no children and where the ages were not to be considered as representing the whole community. Merk's cases were of all ages and not from an institution whose inmates were of any special period of life.

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[1] Bulletin of the Illinois State Board of Health, Vol. V, No. 7, p. 442.

Merk's Table of Ages

From	0 to 5	years	46	cases or	0.9%
"	5 to 15	"	406	cases or	8.3%
"	15 to 30	"	715	cases or	14.7%
"	30 to 40	"	919	cases or	19.0%
"	40 to 50	"	1017	cases or	21.0%
"	50 to 60	"	868	cases or	18.7%
"	60 to 70	"	638	cases or	13.1%
Over	70	"	228	cases or	4.6%
			4836		100.3%

FIG. 5. — PROFESSOR SAMBON AND UMBERTO PAVINATO, AGED 3. (Progress Report, pp. 53 and 74. By courtesy of Professor Sambon.)

It will be noted that the period of life between thirty and fifty years suffers most, but it will also be noted that no age is spared.

Christoferetti [1] reported five cases of pellagra. The ages ranged as follows: 17 months, 7 months, 40 days, 10 months, and 5 months.

As a rule children are not seriously affected, the malady oftentimes being overlooked and the child never reaching an institution. I have seen only one fatal case in childhood; the patient was a negro girl of eleven years. In the first cases in North Carolina, Bellamy [2] lost three cases in one family but at that time all cases were fatal. The majority of our cases were in barefoot children whom we ran down in our search for other cases, and while our experience with cases at this age was considerable, seldom was medical aid sought for them. Marie [3] states that the age most affected is from 20 to 40 years but that children are not exempt.

The question of sex has always been counted of great importance in the study of pellagra. It is interesting to note the following table from the report of the Tennessee State Board of Health Pellagra Commission: [4]

Total Cases	316
Male Whites	98
Female Whites	200
Male Colored	4
Female Colored	14

Lavinder found more cases among female negroes. This has not been my experience to any marked degree. It is usually considered that the female is peculiarly susceptible and the Tennessee report above would tend to bear out this idea. One writer, drawing conclusions from a few cases, thought it was peculiarly a disease of men. It may be said that the influence of sex is trivial with a slight preponderance of females affected.

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[1] Christoferetti, Dr. Leonello, in "Ein Beitrag zur Kenntnis von der Entwicklungdauer der Pellagra," von Dr. Ludwig Merk.

[2] Bellamy, R. H., *Jour. Amer. Med. Assoc.*, 1909, Vol. LIII.

[3] Marie, "La Pellagra," translated by Lavinder and Babcock, 1910.

[4] "Pellagra: A Report upon 316 Cases of this Disease by the Commission appointed by the Tennessee State Board of Health," Nashville, 1911.

In the southern states the consideration of the relative number of cases in the two races is very interesting. Certainly the means of determining this fact are of very doubtful reliability for the reason that the physician who attends the negro usually has comparatively few cases among the whites except in rural sections where there are usually no negro physicians. The institutions in this section are separate for the two races so that conditions in one might not be the same as conditions in another. It was noted in the Tennessee table that only eighteen cases were negroes, while there were two hundred and ninety-eight whites. My own experience has been that in North Carolina the number of negroes affected has been as small relatively as in the Tennessee report. Certainly the zeists cannot claim anything from this for the reason that maize forms a much larger element in the diet of the negro than in the white. I am inclined to think that the difference is due to the fact that, as Stiles has shown so often, the negro is not so susceptible to hookworm disease as the white, and, in fact, hookworm disease in the negro race is counted a rare condition. Pellagra shows a strong tendency to attach itself to a victim of any chronic disease whose resistance is lowered, and this is especially true of hookworm disease. A large number of the pellagrins in the southern states are also victims of uncinariasis. It is also a fact that the negro in the South is usually better conditioned than the poor white. The reason for this is not apparent.

Pellagra frequently attacks the victims of uncinariasis, as stated above, as well as the sufferers from malaria, tuberculosis, alcoholism, poor hygiene, poverty, pregnancy, and too frequent child bearing. The Tennessee report is again of value; it shows the following:

Hookworm	10	Syphilis	6
Tuberculosis	18	Thyroid disease	25
Mental	4	Indigestion	4
Age	8	Epilepsy	3
Invalid	4	Alcoholism	2
None	186	Other diseases	46

Sambon's [1] reference to this subject is so important that it is herewith reproduced *in toto:*

"Associated infections and other debilitating conditions have a very marked influence in predisposing to the development of pellagra and in rendering its course more rapid and severe.

"In quite a number of cases I found that the manifestations of pellagra had followed upon an attack of some antecedent disease such as enteric fever, malaria, dysentery, rheumatic fever, whooping-cough, cardiac disease, or some other debilitating affection. In women, pregnancy and parturition seem to be very common predisposing causes. In one patient traumatism appeared to have determined the outbreak of the disease. Many other diseases are similarly influenced by antecedent or concomitant maladies. It is well known that a latent tuberculosis may be suddenly awakened into activity by an attack of enteric fever or measles, that in children suffering from whooping-cough the rubeola eruption is remarkable for its intensity, that pulmonary tuberculosis, pneumonia, erysipelas, run a rapid course in diabetics, whose glucose-steeped tissues seem to attract every kind of pathogenic organism just as their 'honey urine' attracts ants.

"With regard to the part played by malaria, Doctor Severi, health officer of Torgiano, Perugia, gave me a very interesting example. He said that in 1880 the Chiagio, a tributary of the Tiber, overflowed its banks and gave rise to a large swamp, which was allowed to stand for over eight years. The swamp brought about the appearance of a prodigious number of toads, which on certain days literally covered the highroad to Bettona, and the diligence was obliged to drive over them, crushing thousands of their puffed-out bodies. At the same time, swarms of mosquitoes arose, and malaria broke out and lasted until 1888, when the course of the Chiagio was deviated and the swamp dried. The malaria epidemic was immediately followed by an unprecedented increase in the prevalence and severity of pellagra.

[1] Sambon, L. W., "Progress Report on the Investigation of Pellagra." *London Jour. of Trop. Med.*, 1910.

"At the Pellagra Congress held at Bologna in 1902, Professor Devoto stated that in Mantua in March, 1901, the Po gave rise to serious inundations, which were followed by numerous cases of malaria and, consequently, owing to the lowered resistance, by a notable recrudescence of pellagra.

"In most of the pellagra districts visited by me, malaria is practically unknown, therefore, only in one case have I been able to observe the co-existence of the two diseases — a well-marked pellagrous rash in a young man who presented a fever of decided tertian type and *Plasmodium vivax* in his blood.

"Ankylostomiasis is another affection undoubtedly of importance as a predisposing factor. It is true that ankylostoma eggs are not infrequently found in the feces of patients presenting only a slight pellagrous rash, but I am convinced that ankylostomiasis, and especially a severe form of the infection, must play a very decided part in the development of pellagra, as it certainly does in kala-azar, beri-beri, and other diseases."

Sambon's experience in Italy has certainly been ours in North Carolina and probably throughout the southern states, wherever careful study of the cases has been made. One of the first cases seen by me, which is represented in Figures 2, 3, and 4, was one of a severe malarial infection. The malaria was thought to be the cause of the skin lesions and reported thus: "A Mixed Infection with Tertian and Quartan Malaria Occurring in a Patient with Symmetrical Gangrene."[1] The occurrence of this combination of quartan and tertian parasites had never before been noted in this country and was thought to explain the curious condition with which none of us were familiar. This is only one of a large number of instances of this occurrence of malaria either coincidentally or as a predisposing cause of pellagra. It is very probable that the occurrence of large numbers of cases of pellagra in certain of the mill towns of the South is favored by the presence of hookworm disease. Many of my own cases presented this infection and in some cases it was very severe. There are many other parasitic dis-

[1] Wood, E. J., *Jour. Amer. Med. Assoc.*, Dec. 7, 1907, XLIX.

eases which in the same manner predispose the patient to pellagra. Figures 6, 7, and 8 and Chart II are from a patient who, during her stay in the James Walker Memorial Hospital under my care, passed over one hundred round worms. William Allen [1] of Charlotte, North Carolina, found monads in the stools of five out of seven pellagrins and concluded that these patients were peculiarly liable to intestinal parasitic infection. Four out of five cases studied by him showed the presence of small ameboid organisms in the stools. He found no larger amebæ present and was uncertain whether or not these organisms belonged to the amebæ family, or were monads in the prefusion stage, or were ameboid cells from other sources. He considered that there was great likelihood of mistaking amebiasis for pellagra because of the presence in both diseases of diarrhea and stomatitis. In such cases the occurrence of a considerable eosinophilia would point to intestinal parasitic infection.

The part played by heredity in pellagra has been considered elsewhere and is a matter of importance, but the disease is too recent in the United States for us to draw any first-hand deductions, and until the next generation we must rely on the opinion of European observers entirely. Albera (1781) and Odoardi (1776) considered the disease hereditary and Strombio, the elder (1794), considered it so because so many pellagrins were the children of pellagrins. But, as the children of pellagrins are not all attacked in every instance, he concluded that it was both inherited and acquired. Sambon [2] quotes Zecchinelli (1818) in this connection:

"No one doubts any longer that pellagra is a hereditary disease since it may be clearly seen affecting whole families, more especially within those districts in which it has longest prevailed, as in the districts of Cesana, Limana, Arsie, Quero, and Alano (in the province of Belluno). So far, however, hereditary transmission has been observed to occur solely amongst the lower classes, which are everywhere extremely poor. Hitherto, hereditary pellagra has

[1] Allen, W., "Amœbæ in the Stools of Pellagrins," Trans. Nat. Cong. on Pellagra, 1909.

[2] Sambon, L. W., Progress Report, etc.

not been observed in prosperous families which have remained almost entirely free from the disease even though placed in the very midst of the most severely affected populations. If at times a pellagrin has been seen in families not really poor, besides being a very rare case, it was always the only case in the family. For pellagra to be transmitted by heredity it is necessary, even amongst the poorest families, that one of the parents be in the last stages of the disease. And for the disease to be transmitted to newborn infants, it is necessary, indeed indispensable, that the pellagrin parent be the mother, either pregnant or suckling."

Soler (1791), Facheris (1804), and Marzari (1815) opposed the theory of heredity, but one of them, at least, admitted the predisposing factor of heredity. Lombroso (1892) [1] mentioned two forms of hereditary pellagra. One was mild and the other severe. The first, he said, was a true " pellagra-sine-pellagra," while the second appeared in the second year and was characterized by desquamation, pyrosis, epigastric pain, voracity, uncertain gait, fearfulness, diarrhea, a form of jaundice similar to that seen in malaria, and deficient and retarded development. Later all the manifestations of the disease were recorded and there was noted marked resistance to treatment. In some cases he claimed to find malformations of the skull, extraordinary brachycephaly, or dolichocephaly, retreating forehead, mal-position of the external ears, asymmetry of the face, and anomolies of the genital organs. He also thought the disease could be transmitted by atavism to the grandchildren.

Agostini, according to Sambon, says:

" . . . Whilst in the majority of children born of pellagrin parents, the heredity manifests itself by a reduction of the vital energies, a congenital psychophysical weakness, a development always imperfect and irregular, and a peculiar predisposition to respond to the influence of the pathogenic agent pertaining to the surroundings in which they live, viz., the maize poison; in a certain number of patients the degenerative factor having been accumu-

[1] Lombroso, C., " Die Lehre von der Pellagra." Berlin, 1898.

lated in their procreators, brings about the gravest syndrome of somatophysical degeneration such as dystrophic cretinoid, and myxedematous infantilism."

Christoferetti reported a case of pellagra in a fourteen-months-old child. The child was brought to the clinic on October 1 by its mother, who reported that the sickness began in July. This was the fifth child and the father had had pellagra for five years. The mother had been feeble for one year and had always required several months to recover from childbirth. Although a pellagrin she had nursed the child for three months, but since the fourth month the nursings had been supplemented with corn meal cooked with milk and water. At the end of the first year the child began to fail. The condition on admittance was that of typical pellagra. Two of this child's brothers are healthy, but a sister of eight years is hydrocephalic and has had pellagra for three years. With the removal of corn from the dietary improvement was immediate. The observer closed his report with the statement that hereditary pellagra is not scientifically recognized. This case satisfied Christoferetti that corn and not heredity was at fault, and he did not think that any proof of the heredity of the disease could be produced.[1]

Sambon's view seems quite reasonable. He says:

"The belief that pellagra is a hereditary disease is untenable now that we know that diseases are not hereditary in the scientific sense of the word 'hereditary.' There is no hereditary small-pox, no hereditary tuberculosis, no hereditary syphilis, and likewise there can be no hereditary pellagra. Whether pellagra may be acquired *in utero* by means of placental or amniotic infection is a different matter. Several authors have reported the disease in 'new-born' children, but no one has ever described a case in which the infant was born with the characteristic signs of the disease upon it. I have no reason to doubt that pellagra may be acquired *in utero,* but I have never seen a congenital case myself, nor have I ever

[1] Christoferetti, L., "Pellagra in fruehester Kindheit. Gleichzeitig ein Beitrag zur Kenntnis von der Entwicklungsdauer der Pellagra." *Wien. klin. Wochr.,* 1906.

heard of one. According to my experience, antenatal pellagra, if it does occur, must be exceedingly rare. Within the endemic areas, pellagra affects entire families and, as might be expected, the disease is very common in young children and infants, but in such places the children are exposed to the very same influences which engendered the disease in their parents, blood-collaterals, and ancestors. In non-endemic areas, such as Castione della Presolana, in the province of Bergamo, notwithstanding the presence of numerous pellagrins, I was unable to find a single case of the disease among the younger children, whether their parents were pellagrins or not. I examined with special care the children of families in which both parents were pellagrins and had contracted the disease before the birth of the children, but I was unable to detect any sign of the disease in the offspring. Indeed, these children differed in no way from the children of non-pellagrin parents living in the same locality.

"Both physicians and peasants told me of pellagrins whose elder children, born in a pellagrous district, were also pellagrins, whilst the youngest, born after removal to a healthy locality, were entirely free from the disease. On the other hand, it has frequently happened that in a family the four, five, or more healthy children born in a pellagra-free district acquire the disease all at the same time on taking up residence in a pellagrous locality. I have already mentioned the example of the family Pavinato, in which five healthy children simultaneously contracted pellagra on removing to Frasinelle in the province of Rovigno. Another well-attested fact is that children sometimes become pellagrous first, their parents afterwards. Thus the two sons of Giovanni Ferrario, of Castione della Presolana, contracted the disease in the neighboring Province of Brescia several years before their father, for the simple reason that they both went to work in an endemic locality several years before their father. Although children are very frequently affected, I have often seen patients upwards of eighty years of age who had been pellagrins for two or three years only. Thus Placido Ferrari, of Castione, eighty-one years of age, contracted pellagra three years ago in the province of Brescia soon after taking up field

work, which he had never done before. He has always fed on cheese and polenta. His family consists of eight members, but he is the only pellagrin."

It has been well noted that the degeneracy found in pellagrous districts may be accounted for by other diseases as malaria, hookworm disease, and many other similar chronic diseases.

No phase of the study of pellagra in the southern states has been so interesting as the consideration of the class of people affected and the occupations. In this respect the American experience has been somewhat unique and furnishes rather an interesting departure from the European idea. We often hear the expression of pellagra and poverty being interchangeable terms. In the southern states the extreme poverty of southern Europe is practically unknown. There is no class in this section which at all corresponds to the peasant class of Italy. The negro is usually well fed and comfortably clothed. His condition is probably better than that of the poor white. It is rather difficult to understand why the conditions among the poor whites should be more deplorable than among the negroes in the same locality. The labor situation in the South to-day is such that any man white or black can always find work at good wages. The cotton crop in North Carolina and South Carolina this season was partly left unpicked because pickers could not be had. Any man in the South to-day who will work cannot starve, but another important factor enters at this point: the white man is often unable to work from physical infirmity. It will appear to the reader that the explanation which I am about to give is improbable, but it can be borne out by no less authority than Charles Wardell Stiles as well as many other workers of the Rockefeller Commission for the Eradication of Hookworm Disease. The negro has been shown to be much less susceptible to hookworm infection than the white. Hookworm disease is a problem of great magnitude in the same sections where pellagra is prevailing. There can be no doubt that it is one of the greatest predisposing factors in the production of pellagra. But even in some of the most unhygienic mills of the South where hookworm disease is prevalent as

well as pellagra the economic conditions are far superior to those of the class in Italy which suffers so terribly from this great scourge.

My case records show that the disease is not confined to the poorer element of our population. I have seen pellagra in society women, in teachers, in professional men, in bankers, in wealthy merchants, and in every other walk of life from the least to the greatest. It has always been held in Europe that the disease is almost exclusively limited to the field laborer, and from the earliest writings we learn that Frapolli, Gherardini, and Odoardi as well as many others considered it a disease entirely of the rural sections and that cities were veritable places of refuge from it. Sambon found that the majority of cases examined by him were in field laborers, but even this class was not affected except in the endemic centers. He further claimed that healthy mechanics and workers in other classes of labor than agriculture would become pellagrous when they became tillers of the soil. He found the disease occasionally in coachmen, fishermen, and priests as well as in shepherds, carpenters, masons, and shoemakers, but explained this by the fact that at certain seasons of the year these people would go into the fields to help out in the rush. While pellagra is known to occur quite frequently among the farming people the fact remains that this class is not so universally affected as in Europe. Again, it is interesting to note that in America the disease is often found in the cities. Many cases have been reported from Atlanta, Mobile, New Orleans, Charlotte, Columbia, and other cities. Quite notable is the occurrence of a large number of cases in the thrifty city of Durham, North Carolina, one of the wealthiest cities of its size in the United States. It has never been carefully enough studied to determine just how much time these victims of the cities spend in the country each year. It is a common custom in the South as well as in other sections to leave the cities with the approach of warm summer weather and to seek cooler places in the country.

The table of the Tennessee Commission is quite valuable in regard to the distribution of the disease among the various occupations.

Housewives	141	School Boys	12
None	30	Washerwomen	1
Miners	9	Paupers	1
Laborers	29	Cooks	1
School Girls	22	Miscellaneous	38
Farmers	32		

Pellagra is subject to very definite seasonal variations. This is one of its most characteristic features which has been noted from the earliest description and which is valuable from the standpoint both of treatment and diagnosis. These variations are usually considered recurrences and a recurrence is dated from the appearance of the skin lesions. The time of the year at which this event occurs is subject to great variation, depending on geographical position and the character of the particular season. An early season will bring about the earlier appearance of pellagra while a cold spring will retard the outbreak. I have had cases to appear in every month from March to October but the greater number of cases in North Carolina make their appearance in April and May. In Italy the spring recurrence of the erythema usually occurs in March or April, but it may appear as early as February. The last cases in Italy are said to occur in June. The autumn recurrences occur in September and October. It often happens that a patient who has had the erythema in the spring will have a recurrence again in the autumn. In Egypt the outbreak may occur as early as January. All through the summer months pellagra may be studied in the southern states. As above stated there never occurs a month from March to October without a number of cases. Lavinder and Babcock are authority for the statement that during the months of May and June the number of cases is greatest and they are more severe.[1] In addition to these seasonal recurrences there also occurs very definite exacerbations of the erythema which do not occur in all cases nor at any regular interval. This peculiar manifestation will be mentioned later at some length; suffice it to say that this condition must not be confused with a recurrence. It may be distin-

[1] Marie's "La Pellagra," translation by Lavinder and Babcock.

guished by the peculiar lamellated appearance suggesting the layers of a shell.

The question of the contagiousness of pellagra is naturally a matter of the greatest importance. The question is constantly asked us in the South if pellagrins can be admitted with perfect safety to the wards of the general hospitals. In many places there are restrictions forbidding such cases. No phase of this question is of so great interest to the public as this. From the earliest writings on the subject much has been said in this connection. Strombio, the elder, stoutly denied the statement of some of his predecessors who claimed that the disease was contagious. His logical reasoning did much to dispel the idea of communicability. Since his time little has been said on this subject for the reason that a disease caused by the eating of maize could hardly be considered under any other head than that of grain intoxication. Roussel considered that the problem had been definitely settled for all time and he emphatically stated that pellagra was not contagious. In certain sections of the United States, since the appearance of pellagra, steps have been taken for the establishment of measures for the isolation and quarantine of the disease but this has by no means been general. Lavinder recently wrote:

"If communicable at all pellagra certainly does not seem to be so in any very direct way from one individual to another. Evidence is not lacking that pellagra is possibly a disease of place or locality, somewhat after the apparent nature of beri-beri. This, however, does not necessarily imply anything as to its transmissibility." [1]

Sambon's view regarding this question of the contagiousness of pellagra is summed up by him in his denial of this possibility thus:

"(1) The narrow limitation of pellagra in certain centers, often very small, while there is free communication between their inhabitants and the neighboring population; (2) The almost exclusive

[1] Lavinder, C. H., "Pellagra: A Précis" (Revised Edition), Public Health Bulletin, No. 48.

limitation of the disease to field laborers; (3) The absolute immunity of urban populations, notwithstanding frequent intercourse with numerous pellagrins from the country; (4) The frequent limitation of the disease to only one member of large families living under the most insanitary conditions and sharing the same bed; (5) The absolute immunity of doctors, nurses, and inmates of hospitals and asylums in which pellagrins are admitted; (6) The non-transmission of the disease from wet nurse to child by means of lactation; (7) The failure of all attempts to reproduce the disease by means of the inoculation of the ichorous matter from the skin lesions or the blood and saliva of pellagrins made by Gherardini (1780), Buniva (1805), De Rolandis (1824), and others." [1]

Among the writers [1] who believed that pellagra was transmissible were Van-der-Henvell (1787), Videmar (1790), Titius (1792), Zecchinelli (1818), Hamean (1829), Frank (1842), Botto (1846), and others, as well as a number of American observers of recent times. It is the general opinion in Italy that the disease is not contagious and this view is borne out by the fact that the pellagrins live crowded together within the unaffected areas in miserable huts, but the disease is not transmitted. In recent years the more accurate laboratory work along these lines tends only to substantiate this view. The work of Anderson and also of Lavinder in their attempts to produce the disease experimentally in the rhesus monkey were not conclusive. Recently many autopsies have been performed on victims of the disease in this country without a single case of transmission, and this was the experience of the European observers. All of these facts seem to justify the conclusion that pellagra is not transmissible in the generally accepted sense of that term, and any efforts at isolation seem not only unnecessary but unjust. The fact remains, however, that the question cannot be intelligently disposed of until the etiology is definitely determined. In the report of the Tennessee Commission it will be found that among the cases reported there were one hundred and seven exposures and one hundred and nine cases without such a history. I

[1] Sambon, L. W., Progress Report, p. 90.

have many records in my case book of interesting illustrations which bring up this question of transmissibility. In one house I have seen six cases of pellagra occurring simultaneously. In another house were four cases. A man died under my care with pellagra, and one year later I was called on to treat his wife for the same disease. A woman died from pellagra and in a year her brother met the same fate. If the cause is damaged food it would be a simple matter to explain these occurrences on the ground of a common exposure. If Sambon's hypothesis is proven to be a truth, then we must explain it on the same ground on which we explain the occurrence of malaria. Until the cause is known and understood it will not be possible to answer the question as to whether this is a mere coincidence or whether there is an element of transmissibility direct or indirect to be considered. There can be no doubt of the correctness of the statement made both by Sambon and Lavinder that pellagra is a disease found in certain very definite areas. This accords with the idea of Sambon, who explains this occurrence on the ground of an intermediate host.

The length of the incubation period of pellagra cannot be definitely determined and the views expressed differ according to the number of expressions for no two seem to agree. That it is as long as some suppose can be disproved by the fact that it occurs in infants only a few months old as will be seen from another reference. Sandwith said in this connection:

"It is difficult to fix any incubation period because the onset of the disease is so insidious. But it is perhaps worth referring again to the fact that the maize crop in lower Egypt is harvested in November or December and that the bulk of the patients seem to begin their eruption in January. It is unlikely that the November crop could become so poisoned by the fungus as to produce a skin eruption in January after, presumably, an intervening period of premonitory symptoms. I think we must, therefore, assume that the eruption is the result of poisoning from the previous year's crop or, in other words, that the incubation is perhaps from nine to twelve months' duration."

Merk states that maize alone causes the erythema and that his observation teaches him that from seven to nine months must elapse before the appearance of the erythema. Sambon thinks that the incubation period is about three weeks. His basis for this belief is the fact that an infant of four or five months born in November or December may have the disease. As this is several months before the seasonal recurrence only three months are left to be accounted for, and he subtracts six weeks from this because the child is as old as that before taken to the field. This would place the incubation period at from three to six weeks. Sambon's view is subject to all the criticism of the views of his predecessors and, possibly, to much more. Scheube speaks of a prodromal stage which might be confused with the period of incubation. Certain it is that there is such a prodromal stage which may be, as Scheube says, as much as several years. It is highly probable that during this period, if sought for diligently, there could be found symptoms which would be definite enough to stamp them in the light of subsequent developments, not as true prodromal symptoms, but as symptoms of the developed disease.

There are several types of pellagra and the number will vary according to the individual observer. The chief types, however, are the ordinary chronic pellagra which in America we sometimes find ourselves calling "the Italian form," which means merely that it is the usual type seen in a country where the disease has long occurred and where it has assumed a definite course. This chronic type is subject to many variations. In one case the skin lesion may be trivial while in another universal; in one case the gastric symptoms may predominate, while in another the chief symptom is the diarrhea; or, again, there may be an absence of all gastrointestinal manifestations.

Typhoid pellagra, or typhus pellagrosus, is a term used to designate a condition which is thus given by Belmondo,[1] according to Lavinder:

[1] Belmondo, "Le alterazioni anat. del midollo spinale nella pellagra, etc." *Riv. Sper. di Freniat.*, Reggio-Emilia. 1889 and 1890. XV and XVI, quoted by Lavinder in Public Health Bulletin, No. 48.

"It is rare that typhoid pellagra develops suddenly, for, as a rule, the ordinary symptoms of pellagra show a characteristic intensity; the enteritis and the nervous phenomena (neurasthenia and paresis), as well as the general weakness, assume an unwonted importance, and even on the psychic side there are clouding of consciousness, depressed tone, and a tendency to suicide.

"Most of the cases are poorly nourished and at times much emaciated; however, there are others in which the panniculus adiposus is abundant and the general development of the muscles remains almost normal. There is often almost absolute unconsciousness, at times verbigeration or visual hallucinations of a terrifying nature.

"The entire musculature is in a very pronounced state of tonic contraction, and there is marked rigidity evident on making passive movements of the extremities. In these manifestations the reflex rigidity increases and generally the passive movements ultimately become impossible. Often the patient makes spontaneous, incoordinate movements, especially with the hands and arms, from time to time. In these movements, apparently intentional, there is shown frequently a tremor of the upper extremities, with wide oscillations and a certain grade of ataxia. The speech is drawling, the voice trembling and often nasal.

"The face has a rigid and contracted appearance; however, at intervals the mimic muscles, principally those of the mouth, are agitated by tremors which spread from one muscular fasciculus to another and reach even distant muscles.

"The lower extremities are habitually in forced extension, the feet in plantar flexion. The exaggeration of the reflexes increases up to the last hour of life, the knee jerks being especially exaggerated. Even a definite ankle clonus is not rare. Under a light percussion on the tendon of the quadriceps there is often a spasmodic reaction of the leg, accompanied by convulsive movements of the whole body. At times, together with the plantar clonus, there is a paradoxical contraction of the extensors of the foot, and hyperesthesia to tactile stimuli so marked that a breath of air or a ray of light may provoke motor disorders or tonic convulsions."

As Lavinder says, the name "typhoid pellagra" is most unfortunate as there is no feature of the condition which even suggests typhoid fever, but is an acute explosion which is peculiar to pellagra and occurs as an incident in the chronic course of the disease. There is said to occur a varying amount of fever which at times may be quite high. Death usually follows after from two to six weeks. The accompanying temperature charts show a condition which, while it occurred in pellagra, could hardly be attributed to it. In one case (Chart I) the rises of temperature were undoubtedly due to a coincidental malarial infection as the malarial organisms were unusually abundant and were of the remarkable combination of tertian and quartan types. In the other case (Chart II) no such specific cause could be found except the presence of a large number of round worms, but the extent of the skin lesion which was of the moist variety was so great that there resulted an enormous absorbing surface with a resulting mixed infection. Temperature rise in this case was as much to be expected as in any superficial burn which was allowed to become infected. Typhoid pellagra is usually considered an acute exacerbation of the usual chronic condition — a terminal phase. The description of the European authorities emphasizes the acute nervous symptoms and in such states independent of pellagra the rises of temperature as recorded would not be difficult to explain. I have repeatedly seen this condition. It was well illustrated in the case of a white woman, aged 39 years, who had the typical skin lesions, including the erythema of the face, neck, and arms. Her whole body was in a constant state of tonic contraction. She refused all food, but if it was left within reach she would eat it when left alone. She was possessed with the insane idea that she was not lawfully married to her husband but was living in a state of fornication and adultery. Her statements were so plausible that we accepted them and were amazed later to learn of the error. She became so violent that the restraining sheet became a necessity. Her clothing as well as the bed were covered with blood and crusts which resulted from her incessant movements about the bed. There was a slight rise of temperature. Death resulted after three weeks. This was the

third year of the disease and complied accurately with Belmondo's conception of typhoid pellagra. In the case illustrated in Figs. 6, 7, and 8 and in the temperature chart (Chart I) is seen another

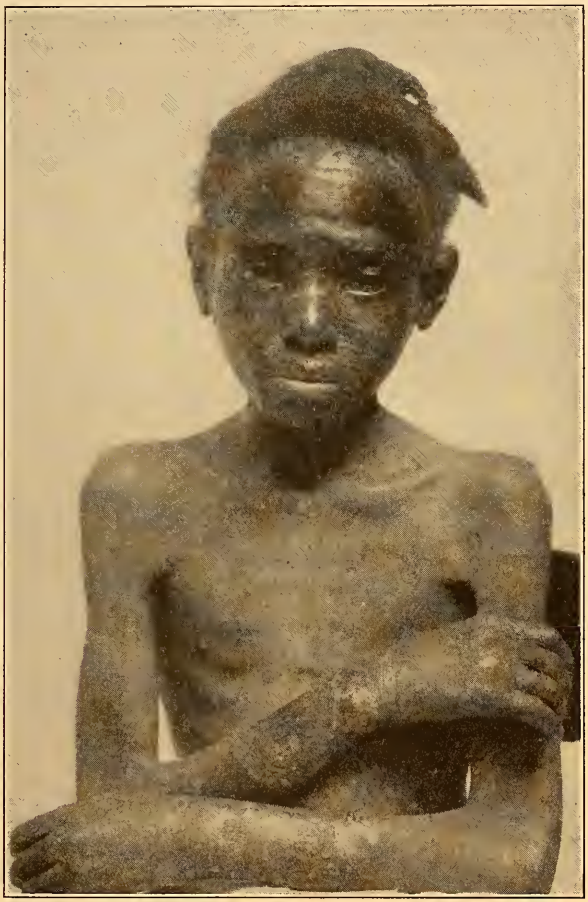

Fig. 6. — An Eleven-year-old Negro Girl with Symmetrical, Moist Lesions of Hands, Forearms, Face, and Neck.

state which in the United States has been confused with typhoid pellagra. In this case the patient had the moist type of the erythema on the hands, forearms, and whole of the face and neck including the external ears. The chart shows the temperature

which I have mentioned above and attributed to a mixed infection by way of the skin. This patient died before there was time for the development of any definite nervous changes. This class of

Fig. 7. — Same Patient as Represented in Figs. 6 and 8, Showing the Posterior Aspect of a Casal's Collar.

cases should be designated as fulminating or acute and should be carefully distinguished from the terminal state of the chronic type of the disease.

Lombroso described seven types of the disease which are men-

tioned merely as a matter of interest but cannot be commended as a classification for the student:

(1) Insane cases.
(2) Those who seek the water for relief from the intolerable burning.
(3) Cases with a tendency to fall backwards.

FIG. 8. — SAME PATIENT AS FIGS. 6 AND 7. NOTE SECRETION BETWEEN THE FINGERS.

(4) Cases in which the patient assumes a bent-over attitude.
(5) Cases with vertigo or fainting spells.
(6) Cases with voracious appetites.
(7) Cases with the skin lesions.

These seven forms of the disease were really recognized in the Venetian pellagrins. The following note by Lavinder and Babcock is interesting:

"Sandwith says he has often seen all these varieties in Cairo, though the second and third are the most rare and the fourth is

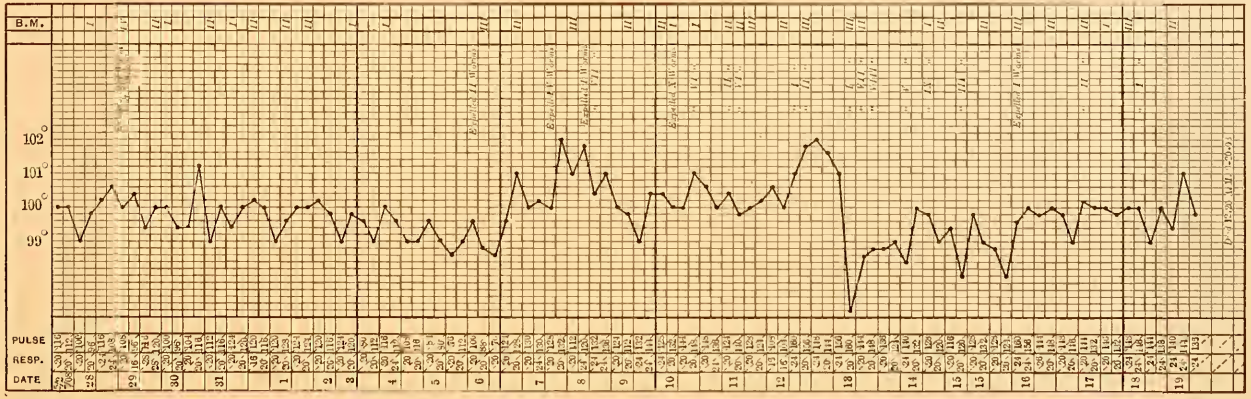

Chart I. — Temperature Chart of Pellagra Patient, Author's Case. (*Jour. Amer. Med. Assoc.*, Vol. LIII, and Transactions of the College of Physicians of Philadelphia, 1909.)

not common. We, too, have seen all kinds in this country, though the second and third are rare in our experience, and the fifth, while fairly common, is not of the severity usually described in Italy. Furthermore, Babes and Sion, in commenting on this subject, say: 'It is true that a popular proverb speaks of different kinds of pellagra, but they do not stand the test of scientific criticism.'" [1]

Mention will be made later of that type of the disease known as "pellagra-sine-pellagra," which signifies pellagra without skin lesions. It seems unwise at this time in the United States for students of this disease to accept such a possibility as a settled scientific fact. After we have acquired more experience with the disease possibly we may become sufficiently trained to recognize such a condition, but at the present, for the sake of conservatism, it would be unwise to make such a diagnosis. Strombio was the first to recognize such a condition. It was seriously questioned by Roussel, who thought that it was merely a stage of the disease in which there was an absence of the skin lesions, but that these lesions had either been present and had disappeared or would appear later in the course of the disease. Lombroso recognized pellagra-sine-pellagra as a congenital form of the disease only. In all of the cases of pellagra-sine-pellagra which have come under my attention it has been possible by a careful investigation to find on the elbows or the forearms or even on the face faint traces of an old erythema which is usually manifested by the remnants of the hyperkeratotic border which is often quite distinct and is always a valuable symptom. Many patients manifest only a very slight erythema which may be readily overlooked even by the patient himself. It must be remembered that the order of the appearance of the symptoms of pellagra may be greatly modified and in some instances the erythema will not appear until very late in the course of the disease. Before the appearance of this pathognomonic symptom the condition is often called pellagra-sine-pellagra.

Roussel divided pellagra into three great heads. The first was pellagra of the first degree, which he called spasmodic pellagra,

[1] Lavinder and Babcock's Translation of "La Pellagra," by A. Marie, p. 182.

and which corresponded to the intermittent form of Strombio. This head was subdivided into beginning pellagra and developed pellagra. The second was the paralytic form or the remittent of Strombio. The third head was pellagrous cachexia, and under this head were two sub-heads: one with eruption which Strombio called the continuous form, and the other without eruption. This latter was merely a resulting cachexia.

The clinical manifestations of pellagra are usually divided into four stages: (1) the pre-erythematous stage, which is usually considered a prodromal stage; (2) the stage of erythema, in which there occur, in addition to the erythema, various digestive disturbances and some central and peripheral nervous disturbances; (3) the stage of severe cerebro-spinal disturbances and psychic phenomena; (4) the cachectic stage, which is usually terminal.

The first or prodromal stage usually begins about Christmas and is characterized by very indefinite symptoms such as anorexia, or voracious appetite, pain, and sensation of distension in the epigastric region, usually diarrhea, though the reverse condition of constipation may occur or the two conditions may alternate. Sometimes there is insatiable thirst or, on the other hand, there may occur an aversion for water. The tongue is thickly coated and later its epithelium is lost. Roussel considered sensations of dryness and burning in the mouth and heat in the stomach to be the first symptom of the disease. Even in this early stage of the disease there occur certain nervous symptoms which usually first manifest themselves with headache of the occipital type, pain in the neck and back, hyperesthesias, dizziness, and muscular weakness, especially in the lower extremities. Vertigo, in this stage, is a common symptom which is much emphasized in the Italian works, but in America it occupies a much less prominent position among the symptoms. Added to these symptoms we often see the typical globus hysterica, formication, uncertainty of motion, increased psychic irritability, ill-temper, and disinclination to work due to marked mental weakness. There is invariably found at this time a varying degree of neurasthenia. This prodromal stage may last only a few weeks

or it may be prolonged into several years. Theodori found it to be four weeks between the appearance of the first prodromal symptoms and the erythema. Scheube found it a varying period subject to remarkable flexibility and was disposed to consider it much longer than usually accepted because he said that the prodromal symptoms were not recognized by the patient in giving a history as connected with the subsequently developing pellagra. Gregor thought that when neurasthenic symptoms lasted for several years without obvious cause pellagra should be suspected. Roussel considered loss of appetite and gastric disturbances to be complications, but dryness of the esophagus, dysphagia, and pyrosis to be the first pellagrous symptoms. Roussel also regarded great hunger, vomiting, cardialgia, and diarrhea as nervous symptoms. It was noted by Babes that often preceding the erythema there was a peculiar redness of the lips and tongue. Lavinder and Babcock noted a peculiar injection of the papillæ of the tongue, which were often pigmented. In the white race it was of an intense crimson and in the negro dark or black. They found it more frequently in the negro and to it attributed the so-called "stippled tongue." In my own cases the changes in the tongue and mouth almost always preceded the appearance of the erythema of the exposed portions of the body, but this is not an unvarying rule as the stomatitis may be entirely absent or may appear some time after the appearance of the skin symptoms. It is a very characteristic symptom and is seldom absent though its time of occurrence may be very irregular. The condition of the mouth and tongue will be dealt with later at greater length. Here it is sufficient to say that there is general redness of the buccal mucosa and at times vesicles and ulcers may be present. Coincident with the appearance of the mouth symptoms or soon after there appears the erythema which gave the name to the disease and which is usually accounted the most important symptom. All authorities are not of the opinion that this is the most important symptom. Sandwith thought it the least important and that it always received an undue amount of attention. In the United States, at least, until we become more familiar with this strange malady, which is certainly new to us, it would be unwise to

attempt the practice of making such a diagnosis without this valuable aid. In my opinion the erythema of pellagra should be regarded as pathognomonic and the diagnosis should never be justified without it or a history of its past occurrence. I have before me as I write a patient who had the digestive disturbances, including the stomatitis with profuse salivation for two months before the appearance of the erythema. The time of the appearance of the skin manifestations is as variable as the time of appearance of the mouth symptoms. There will be found later in this work the record of a case in which the first outbreak of the erythema occurred after the victim had become insane and after all other symptoms had become well fixed. The erythema appears in the spring after the weather has become warm, following the prodrome which is usually described as beginning at Christmas time. Exceptionally the first outbreak of the skin lesion occurs in the fall or winter. A recurrence of an erythema which had appeared in the preceding spring occurs not infrequently in the fall, but it is very unusual for an initial outbreak to occur in the latter season. The distinctive features of this erythema briefly mentioned are symmetry, location on exposed portions of the body, pigmentation and exfoliation. The symmetry is very definite and involves not only symmetry of location but also of shape and size. It will be later shown in more detail just how exact this symmetry is. A skin lesion which does not occur on the exposed portions of the skin, or is not accompanied by such a lesion of the exposed portions must not be considered pellagrous, for the selection of this location is a definite peculiarity of the disease. The first appearance of this erythema strongly suggests simple sun-burn and for the first few days cannot be distinguished from it. In addition to the redness there is often a certain amount of swelling. Following this there occurs exfoliation of the skin, which usually proceeds from the center to the periphery, leaving a border of brownish pigmentation which is the last remnant of the skin condition. This is spoken of as the hyperkeratotic border and is a valuable sign, especially in the examination of a supposed case of pellagra-sine-pellagra. In America two types of skin lesion are recognized: the wet and the dry. They will

be described at length on another page. The most common location of the pellagrous lesion is the backs of the hands. Following this, the lesion occurs on the face, the neck, the feet, and much more infrequently on the unexposed portions of the body as the perianal and perineal regions, the back, the scrotum, and the thighs. At the height of the attack nervous symptoms are commonly found to have already developed. The most usual symptom of this class is increase of the reflexes, though there is often a decided lessening of the reflexes depending, however, on the portion of the spinal cord affected by the degenerative processes. It has been repeatedly noted in the southern states that definite changes in the nervous system do not occur so often as in the European cases. This can probably be accounted for by the fact that in the former location pellagra has not yet entirely assumed the chronic and less severe type as seen in Italy and the patients have been dying before there was time for a definite impression to be made on the nervous tissue. It is no uncommon thing to find an entire absence of changes in the nervous system in such cases.

The period occupied by these symptoms is usually from three to four months. The skin often remains for some time darker in color and sometimes rough and dry. Finally every vestige of the affection seems to have disappeared and many physicians with a limited experience in this disease assume that the treatment instituted by them has been successful and establish unjust claims for certain drugs as a result. But the next spring brings about a repetition of all the symptoms mentioned. This repetition occurs usually each succeeding spring and with each recurrence the severity of the symptoms is increased and a more indelible impress is left especially on the nervous system. I have known cases in which one whole year elapsed without a symptom of the disease only to see a reappearance with the next spring. For this reason alone it is wise to require two years without symptoms before counting a case recovered.

The next stage of the disease is characterized by the appearance of severe cerebro-spinal disturbances. Subjectively the patient complains of numerous parasthesias among which are itching

of the backs of the hands and occasionally of the feet, burning in the epigastrium, scapular region, the feet, the hands, and the arms. This burning is said to cause the tendency for the sufferers to plunge into the water. This weird performance has never occurred in our experience though it is mentioned by a number of the Italian pellagrologers. These patients often complain of formication, sensations of cold, especially in the lower extremities, of globus hysterica, of pain in the neck and the back. Headache of a dull character is often a constant symptom. Tinnitus aurium is a very frequent complaint. Probably the most constant complaint is vertigo. It occurs very often in the American cases, but is not so pronounced as it seems to be in Italy, judging from the literature. Among the more unusual sensations complained of is that of a full uterus.

Objectively the psychical symptoms are very prominent in this stage of the disease. The usual character is that of melancholia. In milder cases there is an interference with thought, slowness of ideas, mild irritable depression, and an aversion to any form of activity (Tuczek). The patient often manifests a great anxiety because of past sins which are found to be entirely imaginary or greatly magnified. There is often the firm conviction of the unpardonable sin. Delusions of grandeur never occur in uncomplicated pellagra at any time. Always the mental attitude is one of profound depression or persecution. The patient will often refuse food to the point of starvation. This is not due to an inability to take food occasioned by the stomatitis which occurs earlier in the disease, but is purely a mental disturbance. Some writers describe a definite suicidal tendency. In our series there was not a single suicide nor were we able to detect any such attempt. Tuczek did not find any tendency for such patients to become dangerous. While our patients are usually very docile and too weak to be dangerous if they so desired, I have seen an attempt on the part of a woman victim to kill a whole household with an axe. Tuczek mentions the occurrence of a circular form of insanity composed of melancholia and mania. This is not unusual in the insane institutions of the South. He also states that he never observed

frank paranoia as did some other observers, but he did see a fatal termination in dementia paralytica.

Certain motor disturbances have been described. Weakness of the muscles, especially of the lower extremities, is sometimes found. Owing to circumscribed paresis of the flexors the extremities may be found in the semi-flexed position. Spasms and painful cramps sometimes occur. Paroxysmal painful tonic contractures in the lower extremities strongly suggesting tetany. Contractures of both lower and upper extremities in the semi-flexed position may occur. The decrease of muscle power may progress to partial paralysis.

Tuczek[1] found the gait paralytic, occasionally paralytic-spastic, but never ataxic. Static ataxia occurs according to him occasionally and incoördination of motion, rarely in the upper extremity. He speaks of this condition having been described as intention tremor. In addition to tremor of the upper extremity tremor of the head and tongue have been described.

Definite epileptiform attacks with loss of consciousness have been observed in rare instances. More commonly the attack simulated cortical epilepsy. In one of my earlier cases the patient died in an epileptiform convulsion after having had three yearly recurrences of the disease.[2]

In this stage the skin reflex as a rule is normal. The pharyngeal reflex is often decreased. The tendon reflexes usually show various deviations from normal. They may be normal, increased even to the point of intense clonic contraction, or, less frequently, decreased. The tendon reflexes in the upper extremity may be increased and in the lower decreased or vice versa. Again, the reflex on one side may be decreased and on the other increased.

The third stage, or the fourth stage if the prodromal period is counted as the first, is the stage of cachexia. It manifests itself with increasing marasmus, atrophy of the subcutaneous fat and muscles, and an inability to resist intercurrent diseases. Weak-

[1] Tuczek, F., "Klin. u. Anat. Studien ueber die Pellagra."

[2] Wood. E. J., "The Appearance of Pellagra in the United States." *Jour. Amer. Med. Assoc.*, LIII, p. 274.

ness is so great that the patient is usually bedridden. Diarrhea is usually very severe and there is incontinence of both bowel and bladder. Death results often from a weakened heart muscle. Sometimes death is due to tuberculosis, and it is a well-recognized fact that pellagrins are peculiarly susceptible to this disease. Edema and effusions into the serous cavities often occur just before death. It is in this period of the disease that the condition previously mentioned as typhoid pellagra supervenes. All the previously mentioned nervous symptoms at this time are exaggerated. Speech is tremulous or drawling; there is marked tremor; the lower extremities are in a state of marked extension and the feet in plantar flexion; the head may be drawn backwards from contraction of the neck muscles, and occasionally it is raised up and moved from side to side in a convulsive manner.

The division of the course of pellagra into stages is purely arbitrary, and there cannot be drawn lines even as definite as in lues. It has already been shown that there is great flexibility in the order of the appearance of symptoms, and in one case frequently referred to in this work it would appear that what has been arbitrarily referred to as the third stage really appeared at the time when the first stage would ordinarily be expected. This patient manifested definite mental symptoms many months before the intestinal and erythematous symptoms.

The blood changes in pellagra are important for many reasons, but more especially because they help to fix the place for the disease in medicine. Hitherto, pellagra has been accounted a grain intoxication belonging to the ergot group. A study of the blood picture will be the greatest argument against such a conclusion. The following blood report was made from a case of a girl of fourteen years brought to London by Sambon.[1] It was a typical case of pellagra.

Red cells	4,850,000
White cells	8,400
Haemoglobin	95%

[1] Sambon, L. W., Progress Report.

Differential leucocyte count:

Polymorphonuclears	56.0%	
Large mononuclears	4.0%	
Lymphocytes	= 37.6%	500 counted
Eosinophiles	0.4%	
Transitionals	2.0%	
Mast cells	0.0%	
	100	

Further notes of this case were recorded thus:

"The shape and size of the red cells were good. No parasites of any kind whatever were noted in the blood. In the differential count it will be noted that the lymphocytes (by that meaning small lymphocytes) are relatively increased.

"This latter condition, a relative increase of the lymphocytes, was further borne out by a series of fifteen differential counts (500 leucocytes in each case) from different cases, the blood of which was brought by Doctor Sambon from Italy. In most of these this was present, and where it was absent there was generally something to account for it, such as a polymorphonuclear leucocytosis due to sepsis or relative increase of the eosinophiles, in all probability due to ankylostomiasis.

"The large mononuclear cells (by this meaning the type of cells usually seen in cases of malaria) were normal or diminished, certainly never increased. The cases where eosinophilia was present all came from an area where ankylostomiasis was prevalent, and this in all probability accounted for it.

"The changes found, then, in differential counts of the leucocytes in pellagra cases may be summed up as follows: In the majority of cases a relative increase of lymphocytes is present; there is no change in the large mononuclear percentage.

"No parasites of any kind were found in any of the specimens of blood examined, this bearing out the work of others. Special attention was directed to the possible presence of spirochaetes, a modified Indian ink method and other stains

being used; but the results were uniformly negative. Nothing of the nature of trypanosomes or other protozoal parasites was ever seen.

" In several thick films of dry blood the hemoglobin was washed out, and the film was stained for filaria. The results again were negative.

" There would seem, therefore, to be little to be gained from the examination of the blood in pellagra, but the failure to find any definite microscopical parasite does not, of course, exclude some ultra-microscopical germ as possibly being the cause of the disease (compare yellow fever, dengue, etc.)." [1]

Fratini,[2] Fiorini and Gavini,[3] and Masini [4] found a definite eosinophilia. The last-mentioned observer stated that the eosinophilia occurred in cycles corresponding to the increase or decrease of the pellagrous toxemia, and he thought it might prove a valuable aid to early diagnosis. My own experience is that all instances of eosinophilia may be accounted for in some other way than by the pellagra. It is so frequent an occurrence for the disease to be complicated by intestinal parasitism, and as the two diseases occur in the same latitude it is not unreasonable to attribute this blood condition to another cause than pellagra. Drewry called my attention to the increase of the mononuclear elements of the blood, but at the time I was inclined to regard this increase as due to intercurrent tuberculosis, which occurred in a number of his cases. My own study of the blood did not impress me with the unusual increase of these elements. In one of the earlier cases there was a remarkable malarial condition and blood slides were made every three hours for a number of days, but the findings, except for the presence of tertian and quartan parasites, were not at all remark-

[1] Sambon, L. W., Progress Report, 1910. p. 107.

[2] Fratini, G., " Il reperto ematologico nei pellagrosi." *Riv. pella, Ital.*, Vol. VII, 1907. Quoted by Lavinder, Trans. Nat. Pel. Cong., 1909.

[3] Fiorini, M., and Gavini. G., " Contrib. allo studio della formula emoleucocitaria nei pellagrosi." *Riv. crit. di clin. med.*, 1905, quoted by Lavinder Trans. Nat. Pel. Cong., 1909.

[4] Masini, M. U., " Il tasso della cellule eosinophile," etc., Gior. di psichiat. *Clin. e tech. Manic.*, Ferraria, 1900, quoted by Lavinder Trans. Nat. Pel. Cong., 1909.

able. The following table of Daniels and Newham [1] is especially interesting in this connection:

No. per c. mm.	Polymorphonuclear. Per cent.	Lymphocytes. Per cent.	Large mononuclear. Per cent.	Eosinophiles. Per cent.
Pneumonia. Great increase up to 60,000	85 to 95	15	5	1
Sepsis. Increase up to 30,000 or 40,000	75 to 90	15 to 25	5 to 10	1
Liver abscess. Increase varies, often slight, 12,000 to 20,000	75 to 85	15 to 25	5 to 10	2
Typhoid. Slight increase at most	50 to 65	25 to 40	5 to 15	1
Malta fever. Slight increase at most	50 to 65	25 to 40	5 to 15	1
Relapsing fever. Great increase up to 50,000	75 to 90	10 to 20	5 to 10	1
Malaria. No increase; decrease during pyrexia	45 to 65	15 to 25	15 to 30	
Trypanosomiasis. No increase	50 to 65	20 to 30	15 to 20	
Kala-azar. Marked increase, 1,000 to 3,000	50 to 60	25 to 35	15 to 20	
Ankylostomiasis. Usually increased, especially in early cases	66 to 70	10 to 20	5 to 10	
Beri-beri. Slight increase, 11,000 to 14,000	24 to 49	30 to 68	1 to 12	
Pellagra. 7,000 to 9,000	50 to 60	32 to 42	3 to 6	

It is rather remarkable that the reduction in hemoglobin in pellagra should be relatively so trivial. With such a degree of cachexia one would expect a much more decided decrease. The following table of Lavinder is of interest: [2]

[1] See Daniels and Newman's work on "Laboratory Methods in Tropical Medicine."

[2] Lavinder, C. H., "Hæmatology of Pellagra," Nat. Pel. Cong., 1909.

Number.	Male or Female.	White or Negro.	Age.	Per Cent Hemoglobin (Dare).	Number White Cells.	Number Red Cells.	Mental Involvement.	Arsenic.	Remarks.
1	male	white	60	75	4,000	3,424,000	no	no	Chronis, mild, neurasthenic.
2	male	white	60	75	8,600	4,684,000	no	yes	Chronic, mild, neurasthenic.
3	male	white	60	64	6,222	4,272,000	no	yes	Chronic, mild neurasthenic.
4	female	colored	52	65	4,508	4,842,000	yes	no	Chronic, mild.
5	female	colored	52	83	10,115	4,824,000	yes	yes	Chronic, mild.
6	female	colored	25	45	6,755	4,368,000	yes	yes	Emaciated, moist erythema, spasticity.
7	female	colored	30	45	4,800	4,888,000	yes	yes	Emaciating, dry erythema; paralytic.*
8	female	colored	25	45	8,266	2,826,640	yes	yes	Emaciating, moist erythema; improved.
9	female	colored	35	38	9,633	2,920,000	yes	yes	Fairly well nourished, dry erythema.
10	female	colored	25	64	13,000	4,148,800	yes	yes	Emaciating; moist erythema; increased reflexes.
11	male	white	39	88	7,066	5,520,000	no	no	Dry erythema; neurasthenic; alcoholic.
12	female	colored	25	38	6,044	3,400,000	yes	yes	Slight emaciation; dry erythema; syphilis; round worms.
13	male	colored	33	95	8,200	5,500,000	yes	yes	Well nourished; much excited; dry erythema.
14	male	white	55	57	11,980	3,800,000	yes	yes	Arterio-scelrosis; dry erythema.
15	female	colored	16	88	13,066	4,636,000	yes	no	Generalized, moist erythema; emaciating paretic.
16	female	white	31	59	10,844	5,604,800	yes	no	Well nourished; dry erythema; paretic.
17	female	colored	22	74	9,754	3,864,000	yes	no	Well nourished; dry erythema; hookworms.
18	female	colored	44	70	17,310	4,708,000	yes	no	Dry erythema; arterio-sclerosis; much excited.
19	female	colored	37	76	5,544	5,008,000	yes	no	Pellagroid; diagnosis doubtful.
20	female	colored	33	96	8,880	4,620,000	yes	no	Cured case; no symptoms for over a year.
21	female	colored	50	93	7,344	4,440,000	yes	no	Cured case; no symptoms for over a year.
22	female	white	25	80	17,400	4,976,000	yes	no	Suicidal and excited; dry erythema; losing weight.
23	female	colored	38	86	12,010	5,504,000	yes	no	Dry erythema; slight loss of weight; mildly excited.
24	female	white	22	60	5,800	4,580,000	no	no	Chronic; mild.

* The word paralytic in this table is used in the sense adopted by writers on pellagra, that is, paretic rather than actually paralytic. Lavinder's Table. From Trans. Nat. Pel. Cong. 1909.

Even more noteworthy is the comparatively normal number of red blood corpuscles. This is found in both the table of Lavinder and that of the Illinois State Board of Health which is here given: [1]

Case No. 1.	Blood pressure. (Stanton.)	Per Cent. Hemoglobin.	Blood.		Case No. 1.	Blood pressure. (Stanton.)	Per Cent. Hemoglobin.	Blood.	
			White.	Red.				White.	Red.
1	...	...	.....	.....	37	164	40	15,000	1,500,000
2	103	55	16,000	2,500,000	38	176	...	.....	.....
3	138	85	9,200	4,250,000	39	118	85	8,000	4,600,000
4	180	83	6,400	3,750,000	40	...	90	25,000	3,500,000
5	205	85	14,000	7,000,000	41	126	85	16,000	3,500,000
6	132	90	10,000	3,500,000	42	164	...	.....	.....
7	...	...	.....	.....	43	175	90	14,000	4,400,000
8	154	75	11,000	3,750,000	44	152	85	9,000	3,250,000
9	...	70	9,000	2,350,000	45	...	80	15,200	3,700,000
10	170	85	6,400	4,500,000	46	155	85	10,000	3,750,000
11	150	70	10,000	3,900,000	47	154	85	12,400	4,250,000
12	134	80	11,000	4,890,000	48	...	95	6,000	4,300,000
13	138	85	12,000	4,720,000	49	140	85	7,600	4,500,000
14	130	60	8,200	5,200,000	50	190	85	16,000	3,000,000
15	162	95	12,000	4,700,000	51	140	89	6,600	3,600,000
16	115	90	20,000	4,500,000	52	120	85	8,000	4,000,000
17	...	95	9,000	4,250,000	53	162	80	12,000	3,500,000
18	132	80	8,500	3,000,000	54	...	80	7,500	3,600,000
19	158	90	11,000	4,350,000	55	152	90	7,000	3,800,000
20	152	...	.....	.....	56	...	89	9,000	4,800,000
21	134	...	.....	.....	57	165	80	12,000	4,000,000
22	123	90	14,000	4,250,000	58	170	85	10,000	3,000,000
23	220	80	8,000	4,000,000	59	138	75	10,000	3,500,000
24	196	90	6,000	3,750,000	60	105	76	3,600	3,220,000
25	...	85	10,000	3,900,000	61	190	95	6.000	4,700,000
26	107	83	9,600	4,200,000	62	170	80	8,600	4,936,000
27	174	75	10,600	3,000,000	63	126	80	8,000	3,800,000
28	150	80	6,000	4,500,000	64	122	55	7,200	1,800,000
29	164	75	16,000	4,700,000	65	134	83	6,000	3,700,000
30	153	50	5,000	3,250,000	66	146	85	8,000	3,750,000
31	184	100	10,000	4,250,000	67	...	..	.....	.....
32	186	85	8,000	3,600,000	68	135	90	10,000	5,000,000
33	132	...	.....	.....	69	180	90	19,400	5,240,000
34	135	90	4,600	4,000,000	70	195	..	.....	.....
35	176	85	10,000	3,000,000	71	160	55	5,000	3,100,000
36	135	75	12,000	3,700,000	72	140	85	9,800	4,500,000

[1] Monthly Bulletin of the Illinois State Board of Health, Oct., 1909, pp. 472 and 473.

Case No. 1.	Blood pressure. (Stanton.)	Per Cent Hemoglobin.	Blood.		Case No. 1.	Blood pressure. (Stanton.)	Per Cent Hemoglobin.	Blood.	
			White.	Red.				White	Red.
73 . .	145	65	8,000	3,750,000	87 . .	180	..	.....	.....
74 . .	160	85	9,200	2,900,000	88 . .	134	85	8,000	3,250,000
75 . .	146	..	.....	.....	89 . .	140	88	11,000	4,700,000
76 . .	120	85	8,000	3,750,000	90 . .	125	78	8,000	3,900,000
77 . .	125	90	8,000	3,000,000	91 . .	145	85	10,000	3,900,000
78 . .	...	90	3,000	3,500,000	92 . .	182	..	.....	.....
79 ..	140	90	8,000	4,500,000	93 . .	130	85	10,000	3,750,000
80 . .	185	..	.....	.....	94 . .	115	90	30,000	5,350,000
81 . .	...	..	.....	.....	95 . .	180	..	.....	.....
82 . .	105	80	4,500	3,700,000	96 . .	108	90	16,000	3,500,000
83 . .	...	..	.....	.....	97 . .	148	..	.....	.....
84 . .	160	..	.....	.....	98 . .	120	60	4,000	3,000,000
85 . .	100	87	5,000	4,850,000	99 . .	138	90	9,000	4,500,000
86 . .	140	80	6,000	3,750,000	100 . .	230	..	.....	.....

There was found such a constancy in the normal proportions of the various blood elements that early in my study blood counts were abandoned.

The following interesting notes on one hundred pellagrins were made regarding changes in the urine (Marie): In 76 cases it was slightly acid; in 14 cases it was neutral; in 10 cases it was alkaline. The urine was more often alkaline in severe cases and paralytics and the aged. In younger patients who suffered from cataleptiform or epileptiform attacks Caldarini observed the same condition of the urine. The latter observer in 33 cases found 21 per cent of the specimens strongly acid, 57 per cent slightly acid, 12 per cent neutral, and 9 per cent alkaline. He found the specific gravity below normal ranging from 1005 to 1010. Various reports regarding the amount of urine secreted in pellagra have been made. Some observers found even at the approach of death there was no decrease in the amount, while others find a decided decrease. Again, some observers find in a large percentage of their cases a trace of albumen; in the work of others there is a notable absence. Ardor urinæ is

a frequent complaint of pellagrins. It is claimed by Marie that in such cases there is also an increase in density and some dysuria, and, further, he claims that in spite of good nutrition there is a diminution of urea, of the phosphates, and of the chlorides.

Indicanuria is a very common and oftentimes constant accompaniment of pellagra. It was found to occur frequently in the earlier days of the study of the disease in this country. It was found by J. J. Watson in South Carolina in a large percentage of examinations. The same experience is reported by the Illinois report on pellagra. It is probable that this very constant presence of indican can be accounted for by the processes occurring in the intestinal tract which have resulted from the changes brought about by the disease.

Eleanora B. Saunders made a careful study of the obstetric and gynecologic features of 24 cases under her care.[1] She shows that 17 per cent of pregnant pellagrins abort; that pregnancy will often precipitate an attack of pellagra. It has been mentioned that pellagrins recover very slowly after childbirth and are often unable to nurse their infants. Vaginitis and vulvo-vaginitis are common occurrences in female pellagrins and have occurred frequently in my cases. Menstrual disturbances are very frequent and are subject to many variations. As Saunders mentions multiparous pellagrins are subject to menorrhagia, which often suggests carcinoma. I have also noted this condition in nullipara and have seen the condition disappear promptly after arsenic treatment had brought about a general amelioration of symptoms. She found amenorrhea in 50 per cent and dysuria in 57 per cent. Leucorrhea is a very common and very persistent complaint. Marie attributed to this disease the large number of stillbirths among the Egyptian Arabs. Saunders emphasizes the importance of refraining from needless surgical procedure in pellagra. I have in mind a woman in good circumstances who developed pellagra in the Johns Hopkins Hospital after a gynecologic procedure and, on the other hand, I recall one of my earlier cases in which the diagnosis was not made at the time, who was treated surgically in the same

[1] Saunders, E. B., Trans. Nat. Pel. Cong., 1909.

hospital by Howard A. Kelly with a splendid effect on the pellagra. This latter patient has never suffered a recurrence.

Eye changes have not been frequent in my experience. A number of my cases have been watched for eye changes by my colleague, J. G. Murphy, but nothing of note has been found. This care in ophthalmoscopic examination was incited by the fact that the use of atoxyl has been thought to bring about serious eye changes. My cases are almost invariably treated with this drug but never without a careful consideration of the possibility of this danger. The following report on the eye in pellagra is taken from Lavinder and Babcock's edition of Marie's work:

"Remarkable peculiarities are found in the eyes of the pellagrous; a falling of the superciliary fold is very frequent in severe cases — even unilateral ptosis is not rare. Inequalities of the pupils are very important and dilatation in the right eye is very frequent. In many cases is found also a marked unilateral injection of the conjunctiva. These are observations which remind one of general paresis, and show, along with other manifestations, how frequently the lesions of the nervous system may be unilateral, especially lesions of the sympathetic system.

"Very often also (74 cases) mydriasis of the two sides is found. Myosis is more rare and when found is more usual in the aged. Cases of blepharitis are not rare as was shown by the Piedmont commission. Often also diplopia, photophobia, and synchysis are found. Many pellagrins remain for years with their eyes closed for fear of the light. Early cataracts are found among the pellagrous; and pterygium is not infrequent. Doctor Ottolenghi, with Professor Manfredi and Doctor Flarer have made ophthalmic studies on pellagrins. Their results are given in the following table:

Number examined	36
Depth of eye normal	12
Changes in the retina	15
Atrophy of arteries	12
Anomalies in fundus of left eye	1
Anomalies in fundus of right eye	6
Atrophy of optic nerve	3
Increase of pigment	3
Dilatation of the veins	1

"Fifteen of these cases showed retinal changes by a yellow or gray reflex in one or both eyes — a sign of precocious senility; it is of interest to note that there were three cases of white atrophy of the papillæ, among which was one case of retino-choroiditis in an advanced stage. Ottolenghi found also in three pellagrins one light case of papillitis, more pronounced in the left eye; in the second case pronounced gray atrophy and diffuse retino-choroiditis of the two sides; the third was normal. It is of interest to note the observation that in several individuals the ocular fundus differed on the two sides. This, however, cannot be given as a reason for the numerous pupillary inequalities since these are noted in individuals who show a normal fundus. However, the unilateral anomalies of the fundus as well as those of the pupils predominate in the right eye and consist in lesions of the arterial vessels with papillary and retinal changes. Rampoldi observed pellagrous ocular troubles principally in the autumn or the spring, and found that they consisted of organic lesions rather than functional disorders. The retina and optic nerve show more than any other part of the eye the pellagrous cachexia; next come the cornea and lens; finally, the choroid and vitreous body. Hemeralopia and pigmentary retinitis are not rare. Torpid ulcers of the cornea are found with essential hypertonus of the bulb and scintillating synchysis of the vitreous."

Whaley found shallow anterior chambers in 33 out of 35 cases examined; there was some dilatation of the pupil, but it was not so prominent a symptom as noted by the Italian writers; in 6 cases was seen photophobia; dilatation of the retinal veins and a yellowish reflex from the retina was noted and the observer had never seen the same condition in any other class of cases. Arterio-sclerotic changes also occurred in all degrees affecting the young as well as the old. Partial vertical homonymous hemiopsia has been recorded.

The senses of taste and smell have been found normal in all cases in which the patient was mentally competent to give intelligent replies.

It has been noted that salivation is a frequent accompaniment

of the stomatitis of pellagra. The salivary glands are usually very active and the saliva is found to be acid.

The study of feces in pellagra by the Illinois State Board of Health showed protozoal infection in 84.8 per cent of the cases examined. This consisted of amebæ and flagellate and encysted forms. It was thought that these protozoal infections account for a large portion of the intestinal symptoms. In another place the work of Allen has been referred to at some length. There seems to be growing up in the South a tendency to attach more than passing attention to the frequency of amebiasis in pellagra and the subject deserves more attention. It becomes a question whether or not amebæ occur in health in the sections where pellagra is occurring and what part they play in a pathologic process after the intestinal lesions of pellagra appear. It would seem that this high percentage of occurrence is more than accidental.

CHAPTER IV

SKIN MANIFESTATIONS

The most important symptom of pellagra is the skin manifestations. Without this symptom, under ordinary conditions, the diagnosis should never be made. This rule should, at least, apply to this country, where the disease is still so little recognized, until a better knowledge is acquired. As a rule, pellagra appears in rural localities where skin diseases are comparatively unusual and the country physician consequently has a more limited acquaintance with such conditions. With this fact in mind it will be attempted in this chapter to consider this group of symptoms more from the standpoint of the general practitioner for whom this work is especially intended. The dermatologist will find it very elementary and from his standpoint open to many serious objections. As a rule pellagra seldom reaches the dermatologist and, further, it should not be considered a skin disease. As far back as the time of Strombio, the elder, the fact was recognized that the skin features were merely the symptoms of a general condition, just as the eruption in syphilis is merely a symptom to be known and recognized by all divisions of the profession regardless of his specialty. The eruption in pellagra is more important even than the eruption in syphilis, because in the latter disease when there is a doubt about the diagnosis, the Wasserman reaction may be resorted to and the result be absolutely relied on. In pellagra there is no serum test.

It is well at this place to consider the question of pellagra without skin manifestations, or the so-called "pellagra-sine-pellagra." This question has occupied my attention for a long time, and I have finally concluded that such an occurrence is highly improbable and that the explanation of such a description

in the literature was to be found in the fact that at times the eruption in pellagra is so insignificant as not to attract attention, even from the patient. It is no unusual thing in securing a history in such cases where there is reason to suspect pellagra that on cross-questioning one will learn that during the past summer the patient did have a rather severe sun-burn which was not of sufficient consequence to be mentioned. It is well recognized that the eruption in scarlet fever may at times be so insignificant as not to be detected until the appearance of an acute nephritis or less frequently until the discovery of a desquamation. Unfortunately, in pellagra the insignificance of the skin lesion in no way indicates a mild attack. Many of the most severe and even fatal cases have the most insignificant skin symptoms, while on the other hand "pellagra universalis," or pellagra with a general distribution of the skin lesion over all or a large portion of the skin surface, may occur in the very mildest cases. In North Carolina there have been more recoveries in cases of pellagra universalis than in any other class of cases. The converse is not necessarily true. We have been told that in the London School of Tropical Medicine the students are taught to diagnose pellagra without the presence of the skin manifestations. Certainly such teaching would be unwise in the southern states, if for no other reason than because of the fact that in this region there also occur sprue, Cochin-China diarrhea, and amebic dysentery. Sprue, especially, complicates the question, for the reason that its symptoms, except for the absence of skin manifestations, are almost identical with pellagra. After a careful study of the two diseases one is unable to distinguish so-called "pellagra-sine-pellagra" from sprue. It is highly probable that cases have been called sprue when they were really pellagra with inconspicuous skin lesions. For the sake of conservatism it is wisest to count the skin manifestations of pellagra as the pathognomonic symptom. It may be that in so doing some cases of pellagra will go undiagnosed, but this number will be gradually reduced as the physician becomes more and more familiar with the disease and the possibility of its occurrence. It will soon be the rule to have this possibility in mind

when examining patients with obscure functional nervous disturbances or depressive mental states, especially when there is added digestive disturbances. In such cases a careful inquiry will often be repaid by the discovery that there was an erythema some months previous, or else there may be found definite traces of an old symmetrical exfoliation. This latter may only manifest itself by the presence of a faint line, which will later be referred to as a sign of the greatest diagnostic value. It should never be overlooked that the skin manifestations of pellagra only occur during a very short period and that the remaining symptoms of both nervous and gastrointestinal type will persist and often call for the greatest care on the part of the physician in making a correct diagnosis. These are really cases of "pellagra-sine-pellagra," which goes to show that this term is oftentimes a misnomer. I have in mind a very typical case of pellagra which I saw through the courtesy of Doctor Bigger of Rock Hill, South Carolina. Some time after our consultation it became necessary to remove the patient to an institution in the North, and I was called on by my colleague to bear him out in his diagnosis, as the authorities of the institution were unwilling to accept the diagnosis without the presence of the skin manifestations. Therefore, it will be readily appreciated that in no other condition is a careful history of so great importance.

The time of the appearance of the skin manifestations in the course of the development of pellagra is subject to many variations. In typical cases the ordinary sequence is for the skin lesions to follow the onset of the stomatitis and diarrhea, though either of these latter symptoms may be wanting. There are many instances where the diarrhea and cachexia as well as gastric disturbances have existed for several years before the appearance of sufficient skin indications to settle the diagnosis. In other cases the erythema may appear for the first time after the commitment of the patient to an institution for the insane. I have under my care a woman who claims to have had diarrhea all her life. She is fifty years old. Certainly for the past five years the mouth and intestinal symptoms have strongly suggested pellagra, but it has

been possible to confirm this suspicion only within the past few months by the tardy appearance of a slight symmetrical erythema of the backs of the hands. One of my first cases was a man who had been demented and committed to an institution for many months before the erythema appeared. His first symptom was mental apathy and confusion. This was followed by diarrhea. The erythema was the last symptom. Another patient had been in an insane institution for several years when she was given a furlough to go home. It was on this visit that pellagra was discovered. Her brother died after having been bedridden many months with dementia, diarrhea alternating with constipation, stomatitis, and emaciation. In this case no erythema was detected, though looked for daily over a period of more than a year. If ever the diagnosis "pellagra-sine-pellagra" was justified, this was the time.

Four years ago a man, aged fifty-six, consulted me on account of an indefinite gastric neurosis. He was frightened away by the mention of the stomach tube for the removal of a test meal and was lost sight of until last June, when he returned. At this time he had the first definite pellagrous erythema of the backs of his hands, accompanied by diarrhea and stomatitis. There can be no doubt that his past vague symptoms were those of an atypical pellagra. In such a case the diagnosis could not have been made until the appearance of the skin symptoms, which were absent until the case had become almost hopeless.

The only feature of the skin manifestations of pellagra that is really distinctive is the symmetry. The character of the skin condition itself may suffer many variations, but symmetry never fails. Without it the diagnosis should never be made. Any asymmetrical skin lesion should be classified differently, for it is not pellagra. Before the consideration of any other feature a pellagrologer examines the two symmetrical parts, it matters not where the skin lesion may be located. An erythema of one hand or one foot is never pellagrous. This symmetry is not restricted to the location of the patch of erythema; it also includes symmetry of size and shape. If a pattern of the skin lesion were

made of one side it would be found to conform exactly, in most instances, to the lesion of the other side. In no other disease does such symmetry occur, and in itself it is almost pathognomonic of the type of skin lesion. It will be found that the lines of demarcation between normal and diseased skin are symmetrical in position and direction. Whatever angle is assumed by this line on the right forearm will be reproduced on the left. If there is a patch of erythema on the right elbow no larger than a split pea it will be reproduced on the left elbow in the corresponding spot and be of the same size and shape. If an exact measurement of the limits of the erythema is made of one side it will be found not to vary by a quarter of an inch on the other side. This is illustrated by measuring from the tip of the styloid process to the upper limit of the lesion and comparing it with the same measurement of the other side. Casal observed this feature, and the copper plate, Fig. 1, in the first chapter, quaintly demonstrates it. Since his time all observers have acknowledged the importance of this feature of the disease and none have ever questioned it. In spite of this fact it is notable that too little importance is attached to it. When the scourge appeared in such serious form in the southern states in 1905, long before it was identified as pellagra, this one symptom was universally noted and suggested to many a nervous origin. Fig. 22 depicts a foot of a man who died of pellagra. There is nothing distinctive of the disease in this picture, and certainly a diagnosis of pellagra would not have been made had this been the only skin manifestation, but there was also a symmetrical erythema of the hands (Fig. 23). There was for a long time a doubt in my mind if this really was a pellagrous manifestation, but observation and the teaching of Merk lead me to accept it, having in mind that the symmetry of the lower extremities is not so marked as in the upper, and also that the other limb showed a much slighter lesion in the corresponding part. It seems that to complete this picture of perfect symmetry the action of sunlight must be added. In the lower extremities the sun seldom having any direct action, the erythema is not so well defined, either as to symmetry or to

the sharpness of the line of demarcation between normal and diseased skin. The attention of the reader is directed to the accompanying diagrammatic sketches showing the areas of skin involvement. It will be noted that this symmetry is strictly adhered to in every instance. These are not selected cases, but are true representations of the conditions as they exist. When in doubt of a diagnosis the chances of error will be greatly lessened if this symptom is held clearly in mind, for such symmetry has never been imitated in medicine. One of my patients had a patch of erythema no larger than the cross section of a lead pencil at the outer canthus of the right eye. The case was watched with unusual interest to see if the symmetry would be carried out. In a few days there appeared at the corresponding position of the other side an area of the same size and shape. It will be noted that the pectoral extension of the Casal collar is placed exactly symmetrically and its tip is exactly in the mid line of the body.

Our knowledge of the location of the pellagrous erythema had its origin chiefly in the writings of the Lombardian and Venetian physicians, and even to-day their view is largely adhered to in many details, though they did not seem to appreciate the importance of the erythema in its unusual positions. Frapolli in 1771 gave a very concise account of the ordinary type of the skin lesions. He described it thus: ". . . . manus denique, pedes, pectus, raro etiam facies, cæteræque Corporis Soli, expositæ partes turpiter foedantur." [1]

Odoardi, who confused the disease with scorbutus because of the affection of the mucous membrane of the tongue and mouth, accepted the account of the Casal collar from a French translation of Sauvage's "Nosology," without tracing it back to its real author. He did, however, begin a more accurate manner of describing the locations of the skin lesions. For example, in place of saying that the lesion was of the hands, he added the more

[1] "Physici Francisci Frapolli Mediolanensis Nosocomii majoris medici animadversiones in Morbum, vulga Pellagra." Mediolani, 1771. See also Merk's "Hauterscheinungen der Pellagra."

exact backs of the hands. We are indebted to him also for first mentioning the feet as a situation for the lesion. His statement that the erythema did not appear in this situation until the disease had existed for three or four years has not been borne out in my experience, for I have seen the feet and legs of children affected with the first outbreak.

Raymond later wrote a more exact description of the skin manifestations in which he described the areas affected and the lines of demarcation between normal and diseased skin. But it was not until some years later that it was recognized that the erythema might appear on the covered portion of the body as perianal and perigenital regions. Merk, to whom we are indebted for the most complete and accurate account of the skin manifestations of pellagra and to whom I am largely indebted for much of the information in this chapter, divides the skin lesions into the usual locations and the unusual locations. This will be adhered to in this chapter for the sake of simplicity.

Next in importance after symmetry is the distribution of the skin lesions. The relative frequency of the various situations is shown in the following table of Merk's:

1679 cases, or 77 per cent, with erythema of the backs of the hands alone.

282 cases, or 13 per cent, with erythema of the backs of the hands and the neck.

164 cases, or 7.5 per cent, with erythema of the neck.

53 cases, or 2.4 per cent, with erythema of other parts of the body.

In a series of my own the following was noted. The number of cases was 189.

182 cases, or 95.3 per cent, with erythema of the backs of the hands.

36 cases, or 19 per cent, with erythema of the neck.

4 cases (all children), or 2.11 per cent, with erythema of the feet only.

It will be seen that the hands are more commonly affected than any other part. In pellagrous countries the physicians, as a rule, are content to base their opinions on the appearance of this part alone. This is well illustrated in the museum specimens of pellagra, which only include the diseased hands and forearms. In 1881 Hardy and Marchand described five cases: four showed the hands alone affected and the fifth showed the tongue. In only 5 per cent of my own cases was the lesion of the backs of the hands lacking, and most of these patients were children, who were accustomed to going without any covering to their feet and legs, thereby exposing these parts to the sun equally as much as the hands. It is safe to say that in this country, at least, not more than 1 per cent of the adult cases fail to have the lesions of the hands.

The erythema of the backs of the hands may occur as round spots about the size of a half dollar, which are separated by areas of normal skin. These areas of diseased skin may become confluent. In other cases the area of skin affected is more spread out, covering the entire back of the hand. Laterally and medially the erythema stops sharply on the line where the sweat glands begin, and does not, except very rarely, involve the palms. This erythema extends up the forearm and ends with a sharp line of demarcation on the extensor surface. Sometimes the erythema extends the whole length of the forearm, while again it may extend only two or three inches above the wrist. In some cases the skin involvement is limited to a chaffing of the knuckles and is often so slight as to attract no attention. In some cases the upper limit of the erythema is situated between the wrist and the carpophalangeal articulations, as is seen in Fig. 10. It is not unusual to see an anterior extension just above the wrist occupying the position of the pronator quadratus muscle. The involvement of the upper portion of the forearm and the arm may occur. It is a generally recognized fact that in women the extent of the skin involvement is greater than in men, and is no index to the gravity of the case, as has been mentioned. The involvement of the forearm is frequently in the shape of a triangle, with the base at the

Fig. 9. — A Row of Pellagrous Hands. (Reproduced through the courtesy of the Illinois Board of Health, Dr. J. A. Egan, Secretary.)

wrist and the apex at a varying point on the external surface of the forearm. Occasionally the lesion extends around the forearm to the anterior surface, being continuous throughout and thereby forming a much larger triangle, which is wrapped around the part.

Fig. 10. — Case of Dr. C. H. Lavinder in the U. S. Marine Hospital at Staple-ton, N. Y. Note limited area of erythema.

Raymond was the first to call attention to the fact that there is a tendency for the last two phalanges of the fingers to be spared by the erythematous process. This observation was not confirmed by the South Carolina observers (Lavinder and Babcock). In North Carolina we have seen many illustrations of this absence of the lesions on the ends of the fingers, but, on the other hand,

we have also seen many cases with the lesions extending to the edge of the nails, resulting, in some cases, in an atrophic condition of the ends of the fingers, which suggests the appearance of the fingers of a cadaver which has lain on the dissecting table for some time. The nails are never damaged by the pellagrous lesions. As a rule the palms of the hands are spared, but even to this rule there are exceptions, some of which I have seen. However, pellagra cannot be said to affect this part but very exceptionally, probably not more than in one-half of one per cent of the cases. In the United States many writers have emphasized the points of the elbows as a frequent location of the erythema. Such has been my experience, but it is important not to confuse it with a simple irritation and roughness of the skin produced by the contact with such an object as a table or arm of a chair. Such mechanical irritation in an emaciated patient especially could be easily confused with pellagrous erythema. The normal skin is often even covered by a callous produced by this means. The "pellagra gauntlet" is often described, but is not as common a finding as one would suppose from the frequency of this reference. In this gauntlet the upper border is at right angles with the arm, passing across the forearm at a point about midway between the wrist and elbow. This is well illustrated in Fig. 6, which shows the lesion on the posterior surface of the forearm. To form this gauntlet the anterior surface must also be involved.

The arm, while not usually affected, does not always escape. When it does become involved the most frequent seat of the lesion is the outer aspect near the shoulder. In one of my cases such a lesion occurred. In this case the erythematous process extended over the whole of the posterior surface of the hands, forearms, and arms, and nearly all the anterior surfaces of the arms except a small area at the elbow. The lesion was of the dry exfoliative type, with the characteristic brown pigmentation. In addition to these areas the process began over the upper portion of the sternum and extended upward and outward, encircling the anterior aspect of the neck. Posteriorly the back was covered by the same lesion from the hair margin to below the angles of the

scapulæ, leaving a central strip of normal skin and also two areas over the shoulders corresponding to those portions covered by the shoulder straps of the chemise. This case was of great interest, for it so well illustrated the part played by solar influence in the production of the erythema. It recalls the experiments in which the observer produced spots of erythema of whatever size and shape he pleased by cutting out such patterns from the garment worn by the patient and exposing the bare skin to the action of sunlight.

More frequently than observed by Merk does the erythema involve the neck in the cases seen in this country. In 19 per cent of my cases the neck was at least one of the locations of the erythema. The lesion here varies greatly. In some cases there are two symmetrical areas on the back of the neck equidistant from the mid line. In other cases the outline of the lesion corresponds to the outline of the exposed portion of the skin, as in cases where a low-cut neck or V-neck is worn. This involvement is not always confined to that portion entirely bare, but may also include a portion which is covered by only some thin form of clothing. In other cases the lesion is limited above by the hair line and below by the vertebra prominens and passes around the neck, meeting in front either as a broad band or else as a gradually narrowing strip. This broad band anteriorly often has extending downward from it over the manubrium a process which was described by Casal. Merk describes the Casal collar as beginning at the nape of the neck a little below the hair margin and passing diagonally around the neck parallel with the lower jaw and several finger breadths from it. On a level with the larynx the two symmetrical processes meet in the mid line anteriorly. The lower border may begin somewhat below the vertebra prominens and keep close to the root of the neck, uniting with the corresponding portion over the upper part of the manubrium. This produces quite a wide collar, which is often characterized by an irregular upper border. Fig. 7 depicts the collar in a negro girl of eleven years. This collar is much more frequently found in women and children than in men. In the latter it is quite unusual. One

of Merk's cuts shows the last remnant of a Casal collar in a man. I have never seen the Casal collar in a man. Merk says that the entire collar may be merely a line hardly a finger breadth in width or it may be incomplete. Sometimes this incompleteness may be combined with imperfect development. The collar may be deficient either anteriorly over the larynx or posteriorly. Whatever portion of the collar is present is distinguished for its absolute symmetry. The process extending downward from the Casal collar over the manubrium is known as Casal's *appendix fasciola.* Above at its origin it is broad, covering the sterno-clavicular region and gradually tapers downward, ending in more or less of a point. It sometimes reaches as low down as the level of the nipple. Merk only observed this appendix of Casal in men, and states that he does not know of its occurrence in women and children. He further states that this collar is never observed alone without a like lesion of some other portion of the skin surface. Five years ago, in my experience, it was an every-day occurrence to find cases with the erythema of the neck, but as time went on the number of such cases became greatly lessened, until now when such a case is a rarity, though the number of diagnoses of pellagra is by no means decreasing.

In one of Zeller's cases reproduced by Hyde there is shown an extension downward from the posterior aspect of the Casal collar. This same peculiarity was seen in one of my female patients, which is represented diagrammatically in Fig. 12. In this case the process was from more than a Casal collar, as the erythema extended over a large part of the back as well as anteriorly over the whole chest wall as low as the mammary region.

The lower extremities are rather infrequently the seats of pellagrous erythema. The cases reported are chiefly from the southern states. In European literature little attention is paid to this location. It has been stated by Merk that the erythema never appears on the feet or legs without an appearance on other portions of the body. I have seen exceptions to this rule in children, and have in mind, especially, the case of a child twenty-two months old with a typical symmetrical pellagrous erythema

of the feet and lower legs, forming the so-called "pellagrous boot." The lesion was absent from all other portions of the body at that time and never appeared later. Usually the line of demarcation proximally of the erythema of the feet passes across the tops of the feet in the malleolar region separating the anterior portion which is affected from the posterior portion which is usually not involved in the process. The heel is never the seat of any form of pellagrous affection. Sometimes the erythema ends itself without involving the toes. In other cases it passes on, including the toes as it included the fingers. Merk noted that the toes were not equally involved. The great toe, according to him, is affected up to the very nail; the second toe only to the first interphalangeal joint; in the third and fourth the uninvolved end is relatively greater; finally the fifth toe remains uninvolved. There are exceptions to this rule, but it may be expected that the great toe will be more involved than any other. Fig. 11 shows the feet of a negro, and here all toes are affected. In patients in bed suffering with erythema in other parts of the body I have watched from day to day with great interest the gradual development of the lesion on the toes. In such cases the great toe does not suffer so much as in the experience of Merk, but relatively I have noted that the fifth toe was more completely covered by the erythema. In the light of Merk's greater experience I would have to regard this condition noted by me as rather exceptional. It is no unusual thing to find the skin of the tops of the feet affected in adult pellagrins who are bedridden and whose feet and legs cannot be exposed to the sun. But in such cases there is a departure from the usual character of the skin affection. This is chiefly seen in the line of demarcation of normal from diseased skin which is not so well defined. The appearance is often that of an inflammatory condition of the lymphatic vessels, with the accompanying streaks extending up the legs. There is nothing distinctive of pellagra in the lesions of this locality, so that in the absence of the lesion elsewhere the diagnosis of pellagra could not be made. As before stated in children who do not wear shoes and stockings, the nature of the

erythema of the feet and legs is the same essentially as in the erythema of the other parts, but especially the hands. The line of demarcation between the normal skin above and the diseased below in such cases is just as sharply defined as in the hand and

FIG. 11. — SKIN LESION OF THE FEET. THE LESION EXTENDS TO THE NAILS. (Courtesy of Dr. J. W. Babcock, Columbia, S. C.)

forearm lesions. In my experience in such cases the symmetry is as marked as in any other part, but Merk found that this was not so well carried out in his cases. He says that the proximal border has various manifestations. In one man he found the lesion winding around the lower leg, as was described as occurring

in the upper extremity. Usually the involvement includes only the foot, less frequently the foot and lower third of the lower leg, and sometimes in children reaches higher towards the knee. A symmetrical patch of erythema above the patella or below it or in both positions frequently occurs. This is illustrated in Fig. 12.

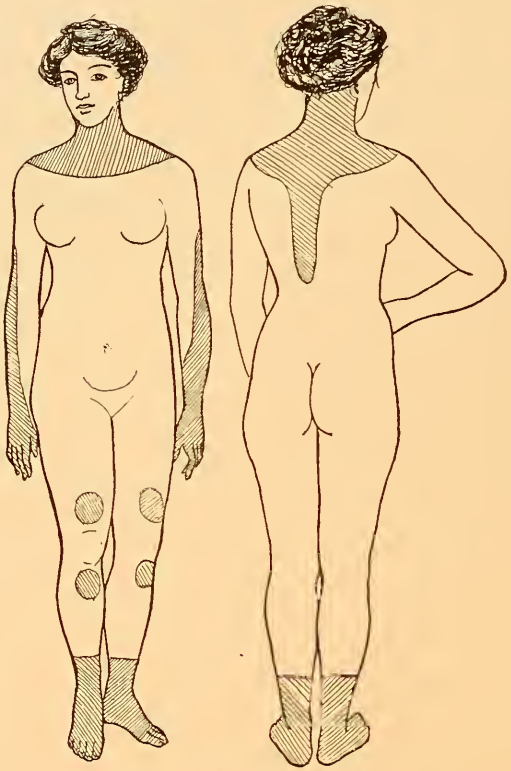

Fig. 12. — Areas of Distribution.

I have known the erythema to occur on the outer aspect of the thigh about the middle and to be as large as two palms. This is very exceptional and deserves no mention among the usual locations.

The lesions of the face are of two kinds. In one, the so-called pellagrous mask, the skin is diffusely affected. In the other the lesion occurs in isolated patches separated by normal skin. The

pellagrous mask may be of mild degree with little deformity, but again it may be of the moist variety with considerable exudation, and then there results more or less contraction of the skin resembling the condition produced by burns. This is well illustrated in Fig. 6. In this case the contraction of the skin was so great that the child had not been able to close her eyes or her mouth completely for weeks. The diffuse type limits itself to the portions uncovered by hair and between the hair margin, and the border of the erythema is a narrow strip of unaffected skin. In the case shown in Fig. 6 the lesion involved the ears and all other portions of the head except the scalp. The extent of the skin involvement differs in different cases. In all cases in this locality the symmetry is especially well marked and there are no exceptions. The most usual location is the ala of the nose, after this the other portions of the nose, then the forehead, cheeks, and chin. Occasionally the lips and more rarely the eyelids and ears are affected, according to Merk. The erythema often has a serpiginous, wavy border, which is well illustrated in some of Merk's cuts. My own cases have more commonly shown a tendency for the formation of spots of erythema. One of the favorite locations for these spots is the outer canthus of the eye. Sometimes there are two symmetrical areas on the forehead of varying size placed equidistant from the mid line of the body. Merk says that the degree of erythematous redness of the face is not often extreme and may be easily overlooked even when sought for. The attention is usually not directed to it until after defervescence, when the brownish pigmentation marks the location and extent of the previous erythema. But even these secondary changes may be so inconspicuous as to be overlooked. This is said to explain the absence of any mention of it in the writing of Casal. Frapolli merely mentions the fact in these words: "... *pectus, raro etiam facies, ... turpiter foedantur.*" Raymond's description was much more accurate, but even he failed to give the location proper consideration. He said: "In children it shows itself on the forehead, the cheeks, the nose. This feature is shown chiefly in women and rarely in men." This

latter observer noted the condition in a Hungarian soldier. In Mexico, Camara Vales noted the fact that the faces of men were more liable to this affection than the faces of women. The pellagrous mask is said never to have occurred independently, but is always found in cases where the erythema exists in some other location. I know of no exceptions to this rule.

According to the authority of Merk the knowledge of atypical localization of the pellagrous skin lesions is of a very recent date. This is accounted for by the belief of the older observers that the action of the sun's rays was essential in the production of the condition. Deiaco was the first to describe the occurrence of the erythematous process on the external genitalia of pellagrous women. Before this, however, pellagrous inflammation of the vulva and vagina was known (Merk). A few years after this publication of Deiaco's he described more unusual localizations, mentioning the fact that Stefanowicz claimed priority in this connection. Merk considers the division into usual and extraordinary to be purely arbitrary, varying with each observer. For example, he says that Raymond would consider the involvement of the skin over the last phalanx of the finger as atypical, while he would consider it usual. Atypical localizations may occur in cases with other typical localizations, thereby rendering the diagnosis much less difficult. Merk includes with unusual localizations a pellagrous mask with a well-defined Casal collar in a man. Certainly this is rightly classified, for it is not possible in such a subject to find a more unusual condition. It has never occurred in my experience. He also describes a perianal lesion which extends from one cheek of the buttocks to the other and from the sacrum to the perineal region. Such a location is not so unusual in the American cases. I have seen erythema in elderly people occupying this exact location which was not pellagrous or even suggestive of it. Hence it is important to apply the rule never to diagnose pellagra by any but a typical skin lesion. Merk also counted as atypical the incomplete Casal collars. Many such cases have occurred in my experience, but their symmetry made the diagnosis simple

Fig. 13. — Dr. Zeller's Case, Showing Remarkable Distribution and the Lamellated Appearance. (Reproduced through the courtesy of the Illinois State Board of Health, Dr. J. A. Egan, Secretary.)

enough. Often the only portion of this collar present consists in two symmetrical areas equidistant from the mid line on the back of the neck. Deiaco [1] described a case in which a strip of erythema appeared over the acromium and covered the lateral half of the entire arm with the flexor and extensor surfaces remaining free. More remarkable than this is a case reported in the Monthly Bulletin of the Illinois State Board of Health (see Fig. 13). As will be seen, the lesion extends from the point of the shoulder on the antero-external surface of the arm down-

Fig. 14. — Atypical Localization on Knees. (After Deiaco from Merk.)

ward to the point of juncture of the middle and lower thirds of the arm. The symmetry of this case as well as Deiaco's is very striking. Deiaco described another case with the involvement on the shoulders entitling it to the term epaulet. Merk gives a diagram (Fig. 14), representing the lesion corresponding to the patella in shape and size with a wavy outline. Sometimes the lesion of the anterior surface of the knee is prolonged downward over the tibia in a sort of tongue reaching to the middle of the lower leg. Again, as seen on one of Merk's beautiful colored plates, the lesion may occupy the posterior surface of

[1] Deiaco, Pius, "Beitrag zur Symptomatologie der Pellagra," *Wiener klin. Wochr.*, 1905, and "Ueber Lokalisation u. Natur der pellagroesen Hautsymptome," 1907.

the knee in the bend thereof. There may be a lesion over the elbow with a tongue extending downward some distance over the ulnar (see Fig. 15).

Fig. 16 shows another of the interesting cases of Merk's in which the scrotum is affected. It is noticeable that on both sides of the raphe the erythema extends outward in perfect symmetry.

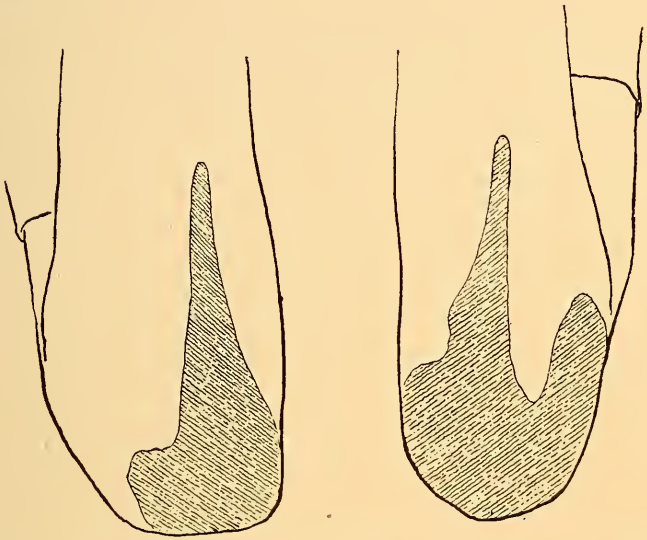

Fig. 15. — Atypical Localization on Elbows. (After Deiaco from Merk.)

Fig. 17 shows diagrammatically a case of my own in a young woman who was not seriously affected and who afterwards made a complete recovery. The skin lesion covered the whole of her back from the lower border of the scapula up to the very hair border of the neck and anteriorly from the upper portion of the breast to the chin. The remarkable feature of this case is that where the chemise shoulder straps crossed the shoulders there was no skin involvement at all. Fig. 12 shows another extensive involvement of the skin of the neck and pectoral region anteriorly and posteriorly, with a tongue extending downward from the posteria area exactly in the mid line. Fig. 18 shows the areas of involvement in a boy of fifteen years. There was

beneath each scapula a sharply defined, somewhat triangular area of erythema distinctly symmetrical. There seems to be no limit to the number and variety of these atypical localizations and a further account of them would be superfluous. Suffice it to say that the lesson drawn from the occurrence of such conditions is

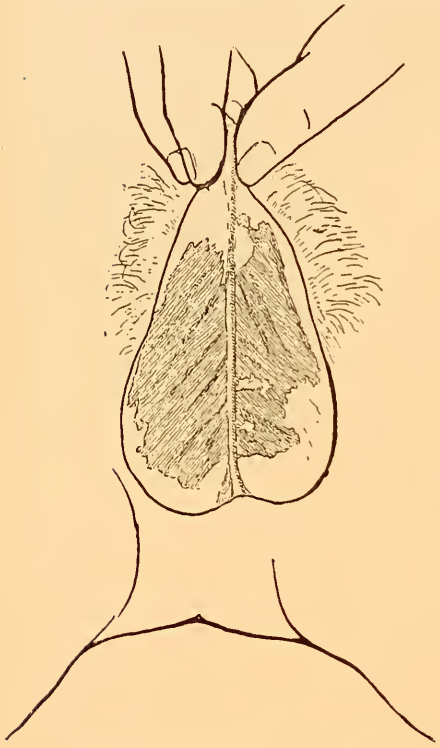

FIG. 16. — ATYPICAL AND VERY INFREQUENT LOCALIZATION ON THE SCROTUM. (After Deiaco from Merk.)

FIG. 17. — EXTENSIVE SKIN INVOLVEMENT. AUTHOR'S CASE. Note areas of uninvolved skin.

that the whole skin surface should be examined in every case of pellagra — not so much for diagnostic purposes, for, as a rule, they are not depended on for such a purpose, but merely from a dermatological standpoint in order that these peculiarly placed erythemata may be classified where they belong. As mentioned on a previous page and depicted in Fig. 22, I have seen such lesions where the only means of identifying them as pellagra

would be that there existed coincidentally other erythematous areas which were typical in their general character and localization.

The character of the skin lesion *per se* is the least important feature, and cannot be depended on in arriving at a diagnosis. It is subject to a multitude of variations of an indefinite character,

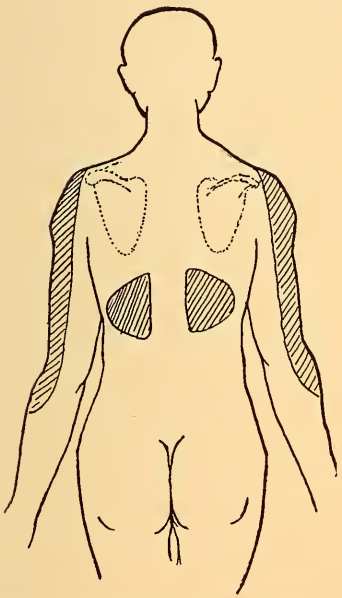

FIG. 18. — AUTHOR'S CASE. Note areas below scapulæ.

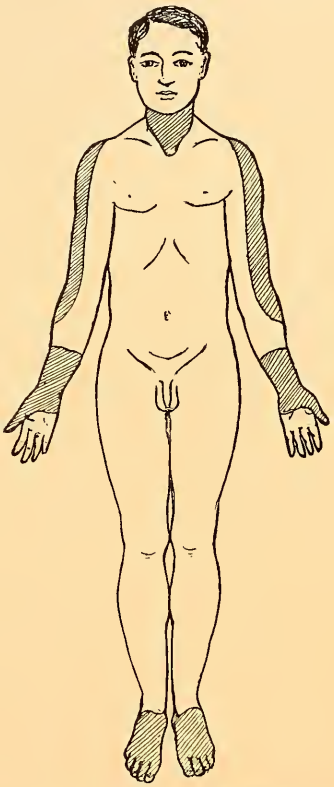

FIG. 19. — AREAS OF DISTRIBUTION. (From Merk after Deiaco.)

lacking that exactness seen in syphilis, though this disease, too, is subject to many variations in form. These forms, however, follow a definite rule and in themselves furnish valuable aid in the diagnosis.

The lesion of pellagra is usually referred to as an erythema, but this term must of necessity be used in a very broad sense

to include all classes of cases. There are probably just as many cases which should rightfully be classified under the term dermatitis. Dyer has pointed out that in a number of cases under his observation the skin changes without regard to localization could be typical of blastomycosis, of the erythema multiforme group, and of a number of other conditions. He distinguished it from vesicular eczema by the appearance and persistence of vesicles in the latter as well as by the development of papillary areas and the marginate, erythematous, elevated, and infiltrated border, all of which point to a deep-seated affection which begins deep and is not merely a catarrhal process started in the mucous layer.

The first change noted is often distinguished with great difficulty from simple erythema of sunburn. Hyde has pointed out that the pellagrous erythema is more reddish than pinkish and that it is rare for this identical shade of color to be reproduced in a blonde by the action of the sun. He also stated that discreet macules often occur which speedily fuse and produce a uniformly smooth, reddened, and distinctly outlined surface suggesting the appearance of a glove when the hand is the portion affected. In a large experience I have never developed such skill that I could differentiate a recent sunburn from a recent attack of pellagrous erythema. Such a distinction requires a keener appreciation of color differences than is possessed by the ordinary general practitioner and must be left to the experienced dermatologist. Not a few cases of solar erythema have been regarded suspiciously by me and my colleagues. I well remember a case of Bellamy's in which he was undecided between the two possibilities for several days, though the child was well nourished and a member of a family living in the very best conditions. Certainly there could not be found a better simile than to compare pellagrous erythema with sunburn, and to one who has never seen the former disease no clearer conception could be had than to fix the mind's eye on the latter condition.

Merk in his work above alluded to says that in the beginning of the skin manifestations there is a preliminary rash of discreet macules which persists from a few days to several weeks.

Some writers say that after a few days the skin becomes covered with scales and exfoliating epithelium. Such is not my experience. As before stated, I have watched the appearance of the erythema from the very beginning in a study of the symmetry of the condition. In this watching for the very first signs of the erythema in the expected locality to conform to the rule of symmetry, the erythema could be minutely studied. There are

FIG. 20. — AREAS OF DISTRIBUTION. (From Merk.)

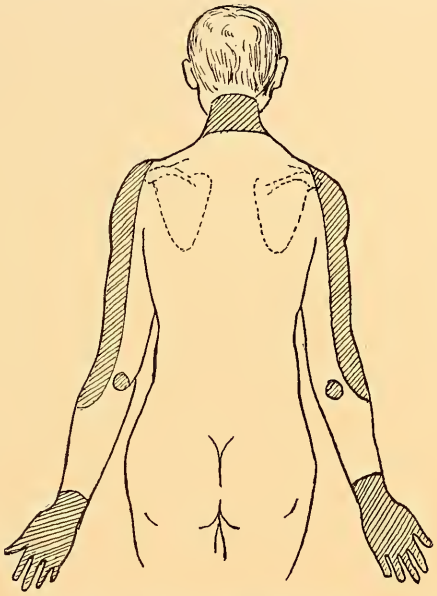

FIG. 21. — AREAS OF DISTRIBUTION. (From Merk's "Die Hauterscheinungen der Pellagra," after Deiaco.)

some cases, doubtless, which follow this rule of Merk's, but there are others which begin as a mere blush without even as much of the macular features seen in the ordinary scarlatina and, in fact, I was unable to detect any macular indications of any kind. Regarding the exfoliation it is certainly not the rule in this country for it to follow so closely on the wake of the erythema. Usually the exfoliation does not supervene until after there is a very definite pigmentation of the skin. Even Strombio stated that after a few days all skin manifestations disappear.

It is apparent that there are cases in which the term erythema truly describes the skin lesion, while there are other cases which even from the beginning cannot be accurately classified under this head. In this connection Howard Fox [1] says:

"The name erythema, by which the eruption of pellagra is generally denoted, does not appear to me to be entirely appropriate. It would seem quite proper to use the term erythema for the first stage of the disease, which resembles an ordinary sunburn, and which lasts only a few days. But it seems somewhat anomalous to speak of the entire eruption as an erythema when the erythematous stage is so comparatively insignificant, while the stage of desquamation is so characteristic and of such long duration. An eruption which is called an erythema conveys the idea of affections such as erythema multiforme or the so-called toxic erythemata, which are not as a rule accompanied by desquamation. The general term dermatitis would be a more appropriate name, in my opinion, than erythema for the pellagrous eruption."

There are many reasons why the term dermatitis would be more appropriate. One of these is, as above mentioned, that only a few cases are true erythemata and it is certain that the skin affection of the vulva, the perineal region, the inner surfaces of the thighs, and even more rarely the scalp could not even loosely be classified as erythemata.

It is largely to the American observers that the division of pellagrous skin lesions into two great groups is due. These are the "wet" and the "dry." After a varying interval of time there is superimposed on the erythema the formation of blebs, which neither in form, appearance, nor size possess any features peculiar to pellagra. Again we can see a marked similarity to solar erythema. I have seen many a case of sunburn occurring in the early summer in a boy who has removed his shoes and stockings for the first time for the summer. Merk says that these blebs are the clinical means of discharging into the upper

[1] Fox, H., "Personal Observation on the Skin Symptoms of Pellagra." *Medical Record*, Feb. 5, 1910.

layers of the corium and epidermis an abnormally increased amount of *Saftzufuhr* and that the lesion takes on the form which is occasionally found in erythema exudativum of Hebra.

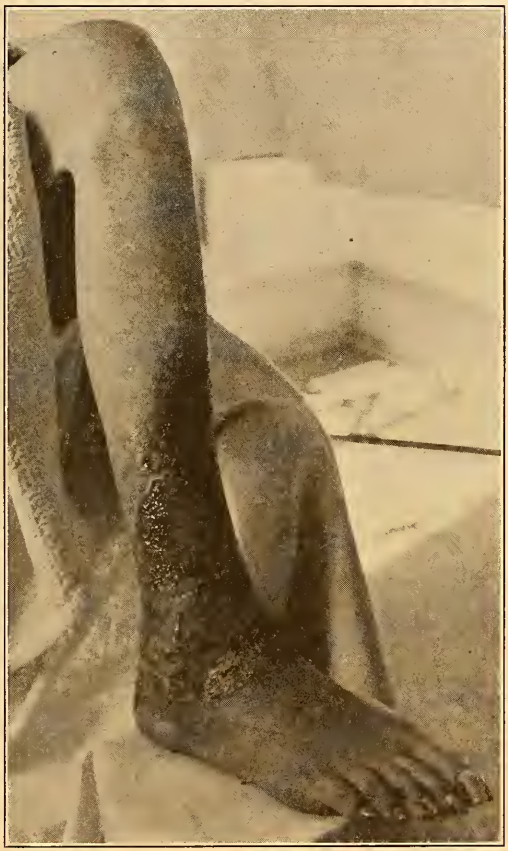

Fig. 22. — Foot and Leg of the Patient whose Remaining Lesions are seen in Figs. 23 and 24.

The seat of these blebs is usually the backs of the hands, less frequently the neck, and in some of my cases in children the legs and feet. The bleb is composed of only one chamber, that is, there are no partitions separating it into subdivisions. Usually the contents of the bleb fully occupies the bleb space and does

not leave a flaccid condition which is sometimes seen in pemphigus. The contents of these blebs is at first, at least, sterile. I have frequently attempted on the various media to grow a culture from this serum, but my efforts were always fruitless. It is not infrequent that the contents of the bleb becomes con-

Fig. 23. — Dry Exfoliating Erythematous Process on Backs of Hands. This patient was affected with malaria—tertian and quartan combination.

taminated from the outside with a resulting pus formation which amounts to the conversion of the bleb into an abscess. In such conditions the underlying skin and that immediately adjacent to it becomes edematous and inflamed and the lymph glands also share in the inflammatory process. This secondary process is not peculiar to pellagra, but is solely attributable to the secondary infection. There naturally results a rise of temperature (see Chart I), which accounts for many of the supposed febrile

cases of pellagra. With the rupture of these blebs containing a sero-purulent fluid crusting results. These crusts have a yellowish green color and, according to Merk, beneath them the epidermis repairs itself and finally assumes the spotted appearance seen in those cases in which the erythematous process did not go on to pus formation. He further states that in other cases the damaged corium and epithelial layer become transformed into

Fig. 24. — Photograph of Same Case Represented in Figs. 22 and 23. Taken immediately after death. Part of a pellagra universalis.

a granulating wound. This is illustrated by the foot lesion seen in Fig. 22. I have never seen this class of cases give rise to such conditions as erysipelas or sepsis. Furthermore, the glandular involvement in these cases of mixed infection never goes on to suppuration. The skin between the blebs is seldom normal. The bleb merely arises from a portion of the erythematous surface, but Merk mentions the possibility of the whole of a Casal collar being transformed into a single bleb, to which condition is given the name pemphigus pellagrosus. In those cases in which the blebs do not become secondarily infected there is a gradual drying up and the surface becomes transformed into a fine crust, beneath which the horny layer may in time regenerate itself. Often the contents of the bleb is lost by mechanical rupture; in such cases the raw and bleeding areas uncovered by skin present the appearance of extensive burns. When, added to this, the patient is maniacal, as often happens, it is very difficult to keep these affected parts protected by any

sort of dressing and consequently the wounds bleed and the whole picture of blood and scabs, added to the general condition of the patient, is unequalled in medicine for its loathsomeness. The most revolting idea which we may conceive of Biblical leprosy cannot compare to the horrors of this form of pellagra. This type of case has caused the discharge in disgrace of more than one faithful attendant of our insane institutions. The reason for this is the fact that after the rupture of the bleb the skin strongly resembles a burn, and this led to the presumption that the attendant had been responsible through carelessness in giving a bath with too hot water. There are many pathetic examples of this.

Merk says that a few days after the appearance of the erythema the surface of the horny layer is found to contain many small fissures, which at first are confined to this layer but later reach the corium. This condition, like the bleb formation, does not occur in every locality where the erythema is found. The location is the backs of the feet and hands. Like the blebs they will heal gradually without leaving any traces if infection does not occur. In the event of the occurrence of infection a granulating wound results, followed by cicatrication. These rhagades or fissures are not infrequently combined with blebs in the same location. Many of the exudative lesions with piled-up crusts have resulted from these fissures in the skin and explain the occurrence of "wet" lesions without the occurrence of a preexisting bleb formation. Often the amount of exudation in such cases is extreme. In maniacal patients these crusts are apt to be rubbed off, leaving a raw surface which would suggest the probability of a preceding bullous condition.

Merk also mentions the occurrence of pustules on the hands and occasionally on the feet. These pustules are said to vary in size from a millet seed to a pea. In some cases a coalescence of these pustules occurs. They may occur on the wrists, but seldom on the fingers. Not infrequently this occurrence is said to complicate the erythema, which may also have been aggravated by the presence of blebs and rhagades. The resulting dis-

figurement is much increased. The erythematous redness which has usually at this stage begun to subside assumes a red color again as a result of the inflammatory process. The hands may be considerably increased in size by the pus and crusts as well as by the inflammatory swelling. The corium is made bare by the process. I have never encountered this condition, but W. F. Hargrove of Kinston, North Carolina, has told me of a re-

Fig. 25. — Pellagrous Lesions of the Hands. (Reproduced by courtesy of Dr. J. J. Watson.)

markable case of his which might be put in this group. The patient was taken sick on the sixth of April with an eruption like chicken pox, lasting about six weeks and extending over the whole body surface. This eruption was more marked on the feet, hands, and face. There was some swelling of the wrists, knees, and ankle joints and a persistent stomatitis, together with a gastroenteritis. She had several hemorrhages from the bowels, two of which were quite severe. Diarrhea was always present. Her mind was clear until the termination of the disease in death,

but there was noted that characteristic retardation in replying to questions. There were enough symptoms to make the diagnosis reasonably clear, but the skin lesions were most atypical. It was thought probable that the initial erythema had been present but had faded before she came under observation. I have never seen a pustule in pellagra, except when it was a bleb that had suppurated. Scheube says that the skin becomes red and swollen, causing the patient to suffer from the tension, as well as the itching and burning. The blebs and pustules dry up and crusts form. This is followed by a desquamation of the epidermis in large patches after a few weeks' duration of the erythematous process. Marie says that occasionally the drying up does not occur, but there develops an edema, followed by bullæ, pustules, and sometimes by gangrene. This is his conception of the "wet" form of the skin lesion. He further says that prior to the recognition of pellagra in the United States such cases were often called dermatitis exfoliativa as well as other similar skin diseases. It was stated above that between the blebs the skin was affected with an erythematous lesion and that these blebs arose from an erythematous base. This is not the experience of all. Some writers say that the skin between the blebs is normal. My own experience has been that the two great varieties, the so-called "wet" and "dry" forms, begin alike and do not separate until after the erythema has existed for some time.

Hyde[1] describes the "dry" lesion thus:

"The hue of the exanthem differs according to the color scheme of the subject and the length of time during which it existed. At first the color is a dull red, which has been likened to the appearance of the skin after common sunburn; yet it is rare that the pinkish hue produced by the rays of the sun in the skin of a blonde subject is precisely imitated. The pellagrous erythema at the outset, generally fading temporarily under pressure, is more reddish than pinkish, displayed at times with dis-

[1] Hyde, James Nevin, "Pellagra and Some of its Problems." *Amer. Jour. Med. Sciences*, Jan., 1910.

creet macules which speedily fuse and produce, on the backs of the hands for example, a uniformly smooth, reddened, and distinctly outlined area, suggesting, when the cuffs have definitely limited the efflorescence above, the appearance of a glove covering the back of the hand. In the milder cases the macular lesions may fade without producing the 'mask' effect; more commonly the eruption persists to a complete involvement of the areas exposed to the light. As the evolution of the erythema advances, the color deepens, refuses to disappear under pressure, and at its height attains a reddish-brown, chocolate, or plum-colored shade, described as 'livid bluish,' a tint at times suggestive of sepia. The first eruptive symptoms may disappear in a fortnight with epidermic exfoliation in light flakes, leaving behind a pigmentation differing according to the severity of the precedent engorgement."

In the same article Hyde says further:

"In most of the first attacks the eruptive phenomena fade in a fortnight, leaving the skin pigmented, roughened, and, in the case of many of the poorer class not under hygienic management, begrimed with dirt. Many, indeed, of the American patients have a recrudescence of the exanthem in the autumn, some under our observation suffering even from repeated attacks in one season; while the type cases of Italian writers undergo a relighting of the morbid process in the skin, only at the succeeding season of spring (second stage), when possibly, without the production of as vivid an exanthem as at the first, the skin again becomes dull reddish in hue, is more deeply infiltrated and, when the exacerbation passes, in cases in which the hands are involved, leaves these organs covered with a seamed, rugous, and irregularly roughened epidermis, which has given pellagra its distinctive title."

The pigmentation of the erythematous areas has been emphasized from the earliest writing and forms one of the most important characteristics. The red color of the erythema gradually

FIG. 26. — NOTE DEEP PIGMENTATION WHICH IS MORE COMMON IN ITALY THAN IN THE SOUTHERN STATES. (Reproduced through the courtesy of the Illinois State Board of Health, Dr. J. A. Egan, Secretary.)

deepens and takes on a brownish tint until finally all semblance of the original erythema is lost. With this gradual change of color of the affected part there occurs also an exfoliation so that there is left an appearance suggestive in the photograph of leucoderma, the contrast being between the fresh skin after the shedding of the affected skin and the brownish areas from which the affected skin has not yet been exfoliated. This is seen in Fig. 23. It has always seemed to me that this pigmentation has been exaggerated, due, doubtless, to the fact that most of our cases have been of a more acute character than the Italian cases. It is always noted that the erythema clears up from the center to the periphery, leaving a brownish "hyperkeratotic" border which is often only a line of light brown color, defining the limit of the previously existing lesion. This line is readily overlooked, even by a careful observer, but when discovered is of the greatest importance from a diagnostic standpoint. Many of our indefinite cases with a history of diarrhea, stomatitis, mental depression, and emaciation were cleared up by the finding of this line. It is especially clearly marked on the neck and the forearm, — those situations where the lesions are well defined.

After exfoliation the skin is soft and velvety, suggesting that of a new-born infant. But with the yearly recurrences of the lesion on the same situation this softness is gradually replaced by a roughening of the skin. After several yearly recurrences of this process the skin atrophies and the tendons are seen standing out distinctly through the thinned-out skin.

In some cases the desquamation occurs in a very different manner, which cannot be said to be characteristic: there is a sort of furfuraceous process, which can readily be confused with other skin conditions, unless the general symptoms are taken into consideration. In such cases pigmentation does not play such an important part.

Hyde mentioned the recurrences of the erythema at short intervals. This has been especially emphasized in our experience. I have seen evidences on a forearm of at least four distinct attacks. The first attack involved an area greater than the second, so that

there is a space between the first and second, as well as a difference in color. The second area is larger than the third in same manner, and the color of the third is not so deep as the second. The final appearance suggests the arrangement of the layers of a shell. This condition is somewhat depicted in Fig. 14. Each of these lamellæ represent an attack of erythema, and for some reason the size of the lamellæ differ in each case, giving this peculiar overlapping appearance.

The occurrence of a hemorrhagic form of pellagra is reported by Strombio, Majocchi, Babes, and Sion, but such a case did not occur in my series. The first interest in this matter was shown in a discussion of the differentiation of pellagra and scorbutus. Merk says that the hemorrhagic flecks seen in the latter disease are very different from the hemorrhagic areas seen in pellagra. The difference is also in location, form, manner of appearance, their continuance, and in the accompanying conditions. Majocchi distinguished pellagra hemorrhagica from purpura. In purpura the points of predeliction are very different from the common seats of pellagra. He said that hemorrhages in the outer mucous membranes in this form were not rare, through which a confusion with pupura is sometimes caused. Even a true intestinal hemorrhage may occur in pellagra. In this connection it should be added that there have occurred fatal intestinal hemorrhages in pellagra without any possible confusion with purpura. Von Scoccia in his sketch of Majocchi's lectures distinguishes pellagra from purpura by the occurrence in the former of the erythema with subsequent pigmentation and desquamation, together with the points of predeliction shown by pellagra.

As a general rule hemorrhagic processes in skin diseases point to a much more serious condition than in cases without them. According to Strombio, pellagra is no exception to this rule.

Merk [1] in an earlier publication than the one which has been

[1] Merk, Verhandl. der Gesellsch. deutsch. Naturf. u. Aerzte Versammlung. 77, 1905, and also a translation of the same in "Pellagra. A Précis" (revised edition), by C. H. Lavinder, U. S. Public Health Bulletin, No. 48.

so frequently referred to summarizes the characteristics of the erythema:

This eruption is an erythema in a dermatologic sense, which can be compared to erythema exudativam (Hebra), as well as

Fig. 27. — Extensive Areas of Involvement of the Posterior Surfaces of the Hands, Forearms, and Arms and a Faint Casal Collar. (Photographed and seen through the courtesy of Dr. J. B. Cranmer, Wilmington, N. C.)

to certain toxic, endemic erythemata like lupine disease in animals (fagopyrismus); also to lathyrism and ergotism.

The eruption appears suddenly, and its genesis is not necessarily connected with atmospheric or solar influences.

Its limitations are peculiarly typical — sharp with red borders

— and as it develops it shows a more or less broad zone of scaling with a peculiar color.

It is days and even weeks before the eruption reaches its height, and even a longer time is required for its retrogression. At first there is a loss of the rosy border, then a gradual fading of the center, while the scaly, crusty zone remains for a long time the seat of the retrogressive process. The changes in the central zone vary with location, but are always characteristic of an erythema.

By its external characteristics the erythema is strongly allied to the so-called hyperkeratosis. But it may show enormous exudation, especially on the backs of the hands.

The erythema is almost always remarkably symmetrical and shows certain points of predeliction, — first on the backs of the hands ("glove"), more rarely the upper surfaces of the feet ("boot"), still more rarely the face ("mask"), and finally the neck ("Casal's neck-band" and "Casal's cravat"); in the second place, the female genitalia and perineal region. It is also seen in asymmetrical, isolated situations, as elbows, knees, and axillary folds.

Some time after its appearance the erythema shows the typical, dirty gray-brown color of changes peculiar to hyperkeratosis. At the same time the bright red of the erythema may be seen through this, and gives to the whole a kind of bronzing, which is especially sharp during the retrogression of the process.

It appears as a rule once annually and this time is usually the spring. It recurs the following year, and finally leads to atrophic changes, especially on the backs of the hands.

The time of the appearance of the skin eruption of pellagra in the southern states is a very variable thing. In my opinion the character of the weather will determine an early or late outbreak of the erythema. As a rule, however, the appearance in the southern states is later than in southern Europe. Many more of my own cases appear in May and June than in April and May. It is no unusual thing for the erythema not to appear until late summer and even well into the fall. Recurrences in the fall after an attack of the erythema in the spring frequently occur,

but are not the rule. There are many cases, as mentioned above, in which repeated exacerbations of the erythema occur on the old lesion before healing is complete. Again, almost immediately after the subsidence of one attack a fresh outbreak occurs. In many instances these exacerbations amount merely to a reddening of the skin with a subsequent tendency for pigmentation to occur. Often these attacks are so trivial as not to be followed by desquamation.

There has been a considerable difference of opinion regarding the pathologic changes produced in the skin in pellagra. This is explained on the ground that the changes are subject to great variations just as are the clinical manifestations produced by them. Very little experimental work has been done on this subject, as the skin changes are not distinctive in themselves of the disease, being merely the changes produced in many of the dermatitides and erythemata. Merk himself had never had an opportunity to study the skin microscopically, and this is the experience of most pellagrologers, due to the fact that pellagrins do not die in the eruptive stage, but usually after the erythema has subsided. In the acute cases which have died under my care the changes were not distinctive, because sufficient time had not elapsed for the impression of the disease to be made on the structure of the skin. Griffini made one of the most important studies of this problem. He examined the skin of three cases. The skin was compared with the skin of an old man. The skin of the first patient was in the desquamative stage and the patient was twenty-three years of age. The second specimen was anemic and the third was in the atrophic stage. In the first case he found the horny layer hypertrophic, the scaling was very profuse and the rete Malpighii showed a decided tendency to hyperplasia. In the second specimen the blood vessels of the papillæ and deeper layers were sclerosed. In the third case there was sclerosis of the vessels of the deeper layers, though in less degree; this same condition was also found in the connective tissue of the corium. He also found an atrophy of the horny layer. The rete Malpighii of these patients showed slight hyperplasia. The sweat glands, hair follicles, and sebaceous

glands were normal. Raymond's results were different. He had studied the skin of an old pellagrin and he recognized only an atrophy of the skin, which is the inevitable result of repetitions of the pellagrous process. He found essentially a thinning of the epidermis and a disappearance of papillæ. The lamellæ were separated by crevices of different length and breadth. The horny layer as a whole was thickened. There was an abundant scaling and especially emphasized was the hyperkeratotic process. The stratum granulosum was composed of small, elongated cells, which did not appear to contain more eleidin than normal. The rete was atrophic and the number and size of the cells were lessened. In many instances the nuclei of the cells were wanting. The papillæ had entirely disappeared. In the corium were vascular tufts, which stood in conspicuous contrast with the atrophy of the epidermis. The hair follicles, sweat glands, and nerves were unaffected. As the skin changes progress he connected the decided hyperkeratosis with atrophy of the rete.

Babes and Sion, according to Merk, examined the skin in different stages. They found in different stages hypertrophy or atrophy. In the earlier stages the epidermis was thickened or thinned, but in the later stages the change was altogether one of atrophy. During the stage of desquamation the epidermis was thickened. The rete Malpighii may be thickened or thinned. During desquamation different layers are well defined, both by color reaction and by structure. This is seen in the stratum corneum where a large meshed network occupies the greater part. Besides hyperemia Babes and Sion found in the skin definite but slight serum transudation, with few leucocytes and a definite metachromatic, homogeneous, and diffuse mass (probably albuminates). There were also found sweat glands rich in cells and metachromatic granulations. Nothing significant was found in the nerves. The changes found in the stage of desquamation and pigmentation are much more important, according to these observers. There is here seen the proliferation of the epithelium, the separate, well-differentiated homogeneous layers being formed of dense or loose material. The inner epithelial layers contain

much pigment of a yellow color. The papillæ in the process of cell proliferation are included and are provided with abundant plasma cells. The sweat glands are proliferated and the enlarged sebaceous glands often contain large colonies of small diplobacteria, and in this location granulation tissue, either diffuse or in foci, is placed. In this same place the plasma and endothelial cells are enlarged. The thickening of the skin is caused by a peculiar underlying tissue composed partly of hyaline material, which is wavy and dense, with broken fibers. There are also found round masses composed in part of exudate and in part of degenerated elastic tissue. In this tissue, which shows in part a reaction for elastic fibers by the Weigert stain and in which, in part, the straining properties with eosin and hematoxylon are quite feeble, there appears in the light blue mass many thick rods, which suggest bacilli stained feebly with the aniline stains. There is also a peculiar condition of irritation and exudation, which in the beginning, at least, can be compared to an erythema from the eating of certain food in individuals who are susceptible. Later a peculiar process appears, which is sclerotic and desquamative and which injures the function of the skin.

Merk remarks that he would have wished to look further into these findings of Babes and Sion,[1] especially into a consideration of the stages in which the various changes were found in order to study step by step the various changes which finally lead up to atrophy and pigmentation. He says in substance:

"Experimental examination of the normal human skin has taught me that the processes in the horny layer, designated partly as hyperkeratosis and partly as parakeratosis, could be due to the normal processes of this layer. From this standpoint it would be interesting to be able to follow out the processes which have resulted in the degeneration and desquamation of the horny layers, and in which histologic change the red color has its origin; the bleb formation, too, might be accounted for in the same study. The only matter about which I am positive is that the exfoliated

[1] Babes and Sion in "Spec. Pathologie u. Therapie von Nothnagel," 1901.

cells of the horny layers do not take the nuclear stain. The condition of that portion containing connective tissue is not mentioned satisfactorily. Raymond found no changes in this part, while Babes and Sion found quite notable changes, especially in the elastic fibers."

The American edition [1] of Marie's work summarizes the study of Griffini thus: ". . . marked atrophy of the stratum corneum, copious desquamation, active reproduction in the Malpighian reticulum and marked sclerosis of the vessels of the papillary layer and the derma."

The skin manifestations of pellagra will ever remain the most important features of the disease from the standpoint of diagnosis until the discovery of some such blood test as the Wasserman or Noguchi tests in syphilis. In the meanwhile, as previously stated, the diagnosis must hinge on the skin symptoms and in their absence, or in the event of only atypical manifestations, the diagnosis should never be made. As formerly stated, the character of the skin lesion *per se* is of the smallest consequence, but even this rule has its exceptions. The photograph designated Fig. 30 well illustrates the importance of this point. This case was properly suspected as pellagra because of the location on a portion of the body exposed to the light and air. The most important feature of the skin manifestations is symmetry; after that the location of the skin lesion, chiefly on the exposed parts; finally, the well-defined seasonal variations.

Merk, after a consideration of all the conditions which in the past had been confused with pellagra, concludes that only the following skin conditions offer sufficient points of resemblance to cause any real difficulty: solar erythema, a strange form of vitiligo, eczema, erythema exudativum multiforme (Hebra), and erythema polymorphe of the author.

It has always been recognized that the sun played a conspicuous part in the production of pellagrous erythema, but in itself could

[1] "La Pellagra," A. Marie. Translation by Lavinder and Babcock. Columbia, S. C., 1910.

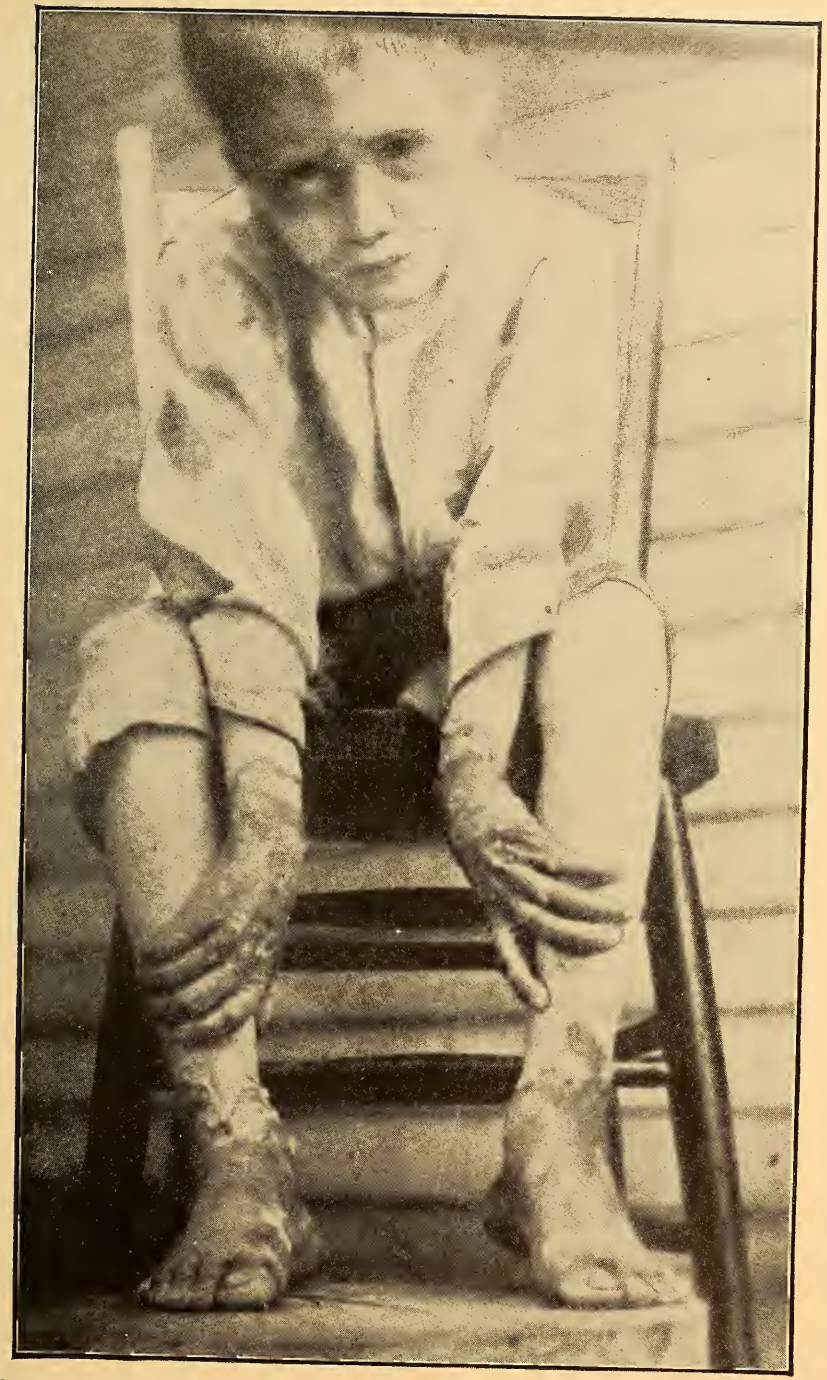

FIG. 28. — BOY IN THE BAPTIST ORPHANAGE. (Reproduced by the courtesy of the Tennessee Board of Health, Dr. Wm. Krauss, Chairman Pellagra Commission.)

never produce it. We can hardly agree with Landouzy and Bouchard in their declaration: "Supprimez le soleil, et vous supprimerez la pellagre." The solar theory received a serious blow when it was conclusively shown by Merk and others that such regions as perineal and perigenital could be the seats of the true pellagrous erythema. There is hardly a portion of the body surface which has not at some time or another been the seat of the disease, but as repeatedly emphasized this does not justify the diagnosis unless there also occurs in certain of the exposed portions of the skin the symmetrical erythema. Merk says that the areas of sunburn or weathered skin are much more extensive than the areas of pellagrous erythema. In this I cannot agree. He also remarks that the experiment of Gherardini in which holes were cut in the garment of a pellagrin and then the patient was exposed to the sun's rays, with the result that areas of erythema occurred, conforming to the holes in the garments, were not conclusive because the same thing would occur if a cachectic patient or an alcoholic and even a healthy individual were exposed to the same thing. Merk further states that in solar erythema the symptoms follow such an exposure and when the part is exposed to the air relief is produced. In pellagra exposure to the air produces a burning which first attracts the attention of the patient to the condition. Again, pellagrous erythema is strictly confined to exposed parts of the body. The differences in color have been referred to on a previous page.

There is a condition seen in men and sometimes in women when they are much exposed to the weather, which resembles that form of chronic pellagra with the dry scaling of the skin. I have noticed it especially in such occupations as oyster shucking and among fishermen. It is readily distinguished from pellagra by the absence of the definite line of demarcation between the normal and diseased skin and by the absence of such symptoms as stomatitis, diarrhea, nervous disturbances, and emaciation.

The confusion of pellagra with vitiligo is a more important matter than would appear on first thought. Could the observer see the erythema of pellagra from the beginning this confusion

would not occur, but, unfortunately, it often happens that the first observation is made during the period of desquamation when many an accomplished dermatologist has made the mistake. Merk says he has observed this condition in women and children, and that it is the form of vitiligo mentioned in the writings of Fox and Darier. Owing to the pigmentary disturbances there is a contrast in the color of the skin of exposed parts with other parts. In the cold months it is said that the pigment is normal, but in the spring there is a decrease of pigment, due to the contact of air with the exposed portions of the skin, and as a result that portion with a lessened amount of pigment has a fresh rose color in sharp contrast to the adjacent over-pigmented skin. This condition often occurs symmetrically on the backs of the hands. Such an appearance is said to resemble strongly the skin of the neck after the subsidence of a pemphigus pellagrosus. Again in this condition an investigation of the general condition of the patient is often necessary to dispel the doubt.

The one skin condition which I most often see, because the patient or his physician suspects pellagra, is eczema. Only a few days ago a clergyman consulted me because of a symmetrically placed squamous eczema on the anterior surfaces of his thighs. Merk pertinently remarks that an error of this kind would be possible only if the backs of the hands happened to be symmetrically affected; that such an eczema would have to run its course in a few weeks and subside without therapeutic aid; that the form would have to be the squamous, with a sharp line of demarcation, with no itching of any note, and an absence of a suggestion of a vesicular stage. He says further that such a form would be theoretically scarcely conceivable, but that practically there is found one or more of these symptoms or even a series of them, though only a very superficial glance would lead to error. Probably the most important point of differentiation would be the brownish pigmentation, which is so often characteristic of pellagra.

Merk finds more similarity to erythema exudativum multiforme (Hebra) than to any other condition of the skin. He

says that the diagnosis cannot be made by a glance, but that the whole course of the disease must be carefully considered. The most important point in this question is the locality of Hebra's disease. He gave as the localities affected the backs of the hands and the feet, and in severe cases also the forearm, leg, arm, upper portion of the thighs, and almost invariably the trunk, and the face; it is never lacking on the backs of the hands where the first efflorescence usually occurs. It will be seen how many points of similarity there are to pellagra. Hebra's pupil, Kaposi, added to the description of this disease by including herpes iris and circinata in the consideration and called the whole group erythema polymorphe. Kaposi taught that changes can occur in the mouth and throat quite similar to the changes produced by pellagra on these same mucous membranes. He also stated that the vulvo-vaginal and urethral mucous membrane might be affected. Besides all this, both Hebra and Kaposi mention the fact of seasonal variations. It is highly probable that some cases of pellagra have been diagnosed erythema multiforme, especially when pellagra is discovered in one who does not eat corn. With care and a consideration of all features of the case there is but small chance of error.

Acrodynia is a disease regarded by many dermatologists as quite similar to pellagra. It is ushered in by symptoms of anorexia, nausea, vomiting, and diarrhea. The face, hands, and feet are found to be swollen, the conjunctivæ injected, and the nervous system affected. These disorders of the nervous system are many and varied. Among them are prickling and burning sensations; at first marked hyperesthesia of the extremities followed by anesthesia. Often there is a complaint of severe pain in the extremities. Early in the disease the eruption appears and presents erythematous spots primarily on the hands and feet, but especially on the palms and soles. It spreads upward on the arms and legs and sometimes involves the trunk. The skin affected is thickened and of a brown color, and finally desquamation occurs. Black pigmentation may follow. It runs its course in a few weeks. In some cases pareses and toxic spasms follow. It is an obscure

disease, thought by many to be a toxemia affecting chiefly the nervous centers. It has been thought to resemble chronic arsenical poisoning. Usually the prognosis is favorable. I had no knowledge of this disease until after beginning the study of pellagra, and while I cannot, therefore, speak authoritatively, I am reasonably confident that several patients have consulted me, suspecting that their trouble was pellagra, when it was really acrodynia. My chief basis for this opinion was the occurrence of the skin lesions on the soles of the feet and the palms of the hands.

Much is said in the literature of pseudo-pellagra, but there is no occasion to consider it here in the differentiation of the skin lesions from those of pellagra, because in my opinion pseudo-pellagra is a misnomer coined for the purpose of relieving the situation for those who believe that the only cause of pellagra is diseased maize. Clinically a study of this condition made famous by the writings of Billod offers no points of difference from the true disease. Manson expresses himself thus: "The disease is pellagra when it fits in with the orthodox theory and when it can be connected in any way with maize, but when this is not possible, the disease becomes pseudo-pellagra." Fortunately, in this country we are not so tied down by tradition to refuse to make a diagnosis, because the etiological factor cannot be accounted for, — that is, even the most ardent of the American zeists will grant such a diagnosis with the clinical evidence before him.

CHAPTER V

THE DIGESTIVE DISTURBANCES

The first indications of pellagra are found almost invariably in the gastrointestinal tract. It will be shown in the next chapter that pellagra may occur without the manifestation of any symptoms referable to the nervous system, and again it will be shown that in some other cases nervous and mental symptoms may usher in the initial attack, but pellagra without an impression on the digestive apparatus has never occurred in my experience. It would be very questionable in my mind if a diagnosis without these manifestations would be justified. In an experience with four hundred cases I have never seen a single case of this kind. It is much more frequently necessary to consider the probability of pellagra without skin manifestations, and as previously stated, at this time, this possibility is not admitted. Allbutt says that dyspepsia is the first symptom to follow the invasion of the pellagra poison. So impressed was Strombio, the elder, with the constancy of these digestive disturbances that he concluded that the origin of the disease was in the digestive apparatus. As stated, the occurrence of a pellagrous skin lesion without digestive disturbances is unknown in my experience, but should it occur the other manifestations would have to be of a very typical character before the diagnosis would be justified. It is much wiser for American students to learn that the disease cannot be diagnosed unless there are present skin, gastrointestinal, and nervous symptoms. In this way error may be avoided and, on the other hand, the patient will be protected because pellagra will never exist very long without the manifestation of the triad of symptoms.

Among the digestive disturbances probably the most unvarying in the constancy of its presence is the stomatitis. When we know

more of the so-called "pellagra-sine-pellagra" it is possible that stomatitis may be shown to be a more constant symptom than the erythema. At the present time it should be placed second in the list of symptoms.

In the series of one hundred cases of the pellagra report of the Illinois State Board of Health it will be noted that mouth symptoms occurred in seventy-two of the cases, hence the percentage without was twenty-eight. This is quite different from my own experience and shows the variation of pellagra in different localities. In my series in only five per cent of the cases was stomatitis absent. It is very probable that in a large portion of those cases reported without stomatitis this symptom would have been noted had the whole course of the disease been observed. Again, in many cases the mouth symptoms are often as trivial as are the skin symptoms in certain instances mentioned previously, and as the skin lesions are often not noted by even the patient so, also, is the case with the mouth symptoms. In many instances to the question regarding the sore mouth the patient replies in the negative, but a careful examination will reveal the presence of a definite inflammation. From this very mild type of stomatitis there are all gradations up to a severe general inflammation of the whole mucous membrane of the mouth and the tongue. In our earlier experience we often considered this condition of the mouth to be due to mercurial ptyalism, which is very common in the South, owing to the frequency of the free use of calomel and blue mass. To distinguish between the two conditions is often impossible.

The sponginess of the gums and the readiness with which they bleed gave rise in the past to the name "Alpine scurvy."

The changes undergone by the tongue and mouth are quite marked. Harris says that the tongue epithelium shows much the same changes as are observed in the epiderm in the affected portions of the skin. Later the epithelial cells are exfoliated around the edge of the tongue, and this process, in some instances, is continued until the whole structure of the tongue becomes bare. But even in the case of the apparently bare tongue on microscopic examination a thin epithelial layer may still be demonstrated.

Furrows are very abundant on the dorsum of the tongue and the redness is general and usually uniform. Ulceration may occur as a late change. This ulceration begins usually on the edges and later may appear on any portion of the tongue surface as well as on the buccal mucous membrane. These changes Harris considers to be identical in most particulars with the changes in the skin.

Sometimes small congested areas are found scattered irregularly throughout the mouth. In these areas the mucous membrane has lost its smooth and brilliant appearance, and the absence of epithelium produces a dark red color. At first these areas are the size of a split pea. This condition has never attracted my attention and I do not regard it as particularly characteristic. About the labial commissure there occur ulcerated areas of a white color; these ulcerated spots are continued to the inner surface of the mouth so that the buccal ulcer is continuous with that of the skin. These ulcers of the buccal mucous membrane are spoken of by one writer as "hyperkeratotic streaks." The buccal mucous membrane may be the seat of a very acute inflammatory process which is characterized by redness, a loss of the brilliant tint formerly seen, together with a roughening of the surface with superficial excoriations and white spots which are encased in mucus. There occasionally occurs vesiculation of the buccal mucous membrane. The tongue is the seat of the same kind of process which is especially marked along the edges.

In the ordinary type of mild case there is nothing distinctive of the condition. The appearance is that of a general redness evenly distributed. Sometimes it suggests to the mind the appearance of the mouth in scarlet fever with the exception that that particular enlargement of the papillæ which goes to make the "strawberry" tongue is wanting and the hue is more of a purple than a red. This redness is especially marked on the hard palate. Babcock has called attention to a peculiarity of the process when it involves this area of the hard palate: a tendency to form a definite line of demarcation of the process, the line being situated at the point in the mouth which marks the limit of an artificial plate for false teeth. I have repeatedly noted this line of de-

marcation and it has been so definite in some cases that a casual glance would make one think that the patient was really wearing a plate. This occurrence is not constant and is wanting in more cases probably than it is present.

In the more severe form of stomatitis the tongue is fiery red and may be edematous. The buccal mucous membrane is intensely inflamed. Ulcers may be found in any portion of the mouth. The secretion of saliva may be so intense that the patient cannot speak intelligibly because of the rapid filling up of the mouth. According to Zeller the inflammatory process may be so severe as to prevent the protrusion of the tongue and to interfere greatly with the taking of food.

The denuded tongue is found to be smooth and glistening and from the color, which is a cardinal red, arose the term, cardinal tongue. Sandwith with equal accuracy calls it the bald tongue. Ulcers do not appear on the tongue until late in the course of the process, and I have observed many cases without any ulceration throughout the whole course of the disease.

Babcock calls attention to small black or bluish black spots on the dorsum of the tongue. This appearance is especially noted in negro patients. Having this appearance in mind Lavinder gave this tongue the name "stipple tongue."

The tongue in pellagra is either pointed and tremulous or it is large from inflammatory swelling and shows the indentations of the teeth.

The salivary glands are often enlarged and tender; this enlargement of the glands and salivation gave rise to the confusion with mercurial ptyalism. The disagreeable odor in mercurial poisoning is much more offensive than in the salivation of pellagra. Watson says that the acme of the stomatitis corresponds to the acme of the skin process.

Usually the first symptom complained of is the sensation of heat in the mouth, throat, and stomach. Taste is impaired and there is marked anorexia.

It is thought that these complaints of heat in the esophagus and stomach are part of a neurosis. I cannot deny that one of the

neurotic symptoms may be this complaint of burning, but, on the other hand, I know that the inflammatory process often extends downward involving a considerable portion of the esophagus. The redness extends throughout the pharynx as far as the eye can see, and a further examination will reveal the process in the esophagus.

The tongue condition together with the intestinal symptoms in pellagra has given rise in some sections of the South to the idea that sprue is prevalent in that region. It is very probable that sprue does occur and this is one of the best reasons for hesitation in acknowledging the possibility of a pellagra-sine-pellagra, for the symptoms of sprue are almost identically those of pellagra without skin manifestations. The matter is so important that the following from Manson's account of sprue in Allbutt's "System" is given: [1]

"Tenderness and often great soreness of the tongue, buccal mucous membrane, fauces, and sometimes of the gullet, depending on a complexity of surface lesions including (a) denudation of the epithelium of the mucous membrane generally; (b) the formation of minute herpes-like vesicles, single or in groups, with an inflamed areola, which quickly rupture, leaving (c) small, superficial but exquisitely tender, ashen-gray ulcers; (d) larger, inflamed, bare, slightly-eroded patches, smooth on the surface usually, or with a slight muco-purulent covering where in contact with the teeth — as when on the inside of the cheeks or lips; often, when on the soft palate, they are markedly granular, probably from inflamed follicles; (e) congestion and swelling of the fungiform papillæ, especially about the tip and edges of the tongue; (f) superficial cracks on the dorsum and edges of the tongue; (g) during complete remission of the acute symptoms, as happens occasionally in most cases, an atrophied state of the entire body of the tongue; this organ then appears pale and almost cartilaginous, with a smooth, glazed surface as if coated with varnish, and completely denuded of papillæ.

"The erosions referred to, sometimes amounting to superficial

[1] Manson, Sir Patrick, in Allbutt's "System of Medicine," III.

ulceration and much sodden by the constant action of the saliva, are most frequently found under the tongue by the sides of the frenum, inside the lips and cheeks; especially where in contact with the teeth, and on the soft palate. The vesiculations ending in the minute gray ulcers are commonest about the tip and edges of the tongue; they come out in successive crops. Activity of both of these lesions is usually associated with increase of diarrhea. In severe cases what I would call the 'psilotic' condition of mucous membrane seems to extend through the entire length of the alimentary canal, affecting the pharynx, esophagus, the anus, and in women, even the vagina."

It is not only in regard to the mouth symptoms that sprue must be considered in connection with pellagra; there are many points of resemblance in all the alimentary manifestations of the two conditions. For myself I can find no satisfactory points of distinction between sprue and pellagra without skin manifestations. In the Transactions of the Pan-American Medical Congress for 1893 is found an article by Cuthbert Bowen entitled "Psilosis (?) Pigmentosa," a disease described as occurring in Barbadoes which is not recognized as pellagra, but an inspecton of the illustrations makes such a diagnosis, in the light of our present knowledge, very plain. There is a splendid water color of the tongue in this condition and another of the tongue in "Indian sprue." The contrast is very striking and of great value in distinguishing the two conditions. In the tongue of the condition which we now recognize as pellagra the papillæ are injected and four aphthous spots on the lateral edges are noted. This tongue is pointed and of a characteristic color, while that of sprue is of a much paler tint and is covered by furrows and ridges. This tongue is represented as larger and rounded at the end instead of being pointed as in the pellagra illustration. Thin says that the salivation described in this Barbadoes condition, which I consider pellagra, does not occur in East Indian sprue.

Some time ago I was interested in a consideration of the possibility of pellagra having existed in our insane institutions unrec-

ognized for some time. Through the courtesy of the late James McKee I was given much valuable information regarding the occurrence of a condition in the State Hospital for the Insane at Raleigh, North Carolina. There was a condition there which was attended with the characteristic skin manifestations of pellagra and a stomatitis. Doctor McKee in describing the condition told me that it more nearly resembled stomatitis materna than any other condition with which he was familiar.

There would be some reason for the confusion of the stomatitis of pellagra with the mouth condition of syphilis, especially when the pellagrous process has advanced to the ulcer formation. The differentiation is made by the lack of the general diffuse redness seen in pellagra and the systemic manifestations. In the past, however, before it was known that pellagra could be found in this country, there was much stress laid on the mouth symptoms of cases that were really pellagra as pointing to a syphilitic condition.

Roussel considered loss of appetite, nausea, and gastric disturbances to be complications of pellagra, but dryness of the esophagus, dysphagia, and pyrosis the first symptoms of the disease. These gastric symptoms as well as cardialgia, hunger, diarrhea, and vomiting he considered of nervous origin. Many patients suffer from great thirst while others abhor drink of any kind. Eructations and other symptoms of the so-called nervous indigestion are frequent. Usually the patient has been under the care of the physician for a number of weeks suffering with vague and indefinite gastric symptoms before the appearance of the stomatitis and erythema. The gastralgia which occurs may sometimes be mistaken for the gastric crises of tabes dorsalis. Procopiu, according to Lavinder and Babcock, says it may cause gastric intolerance, and occurs in paroxysms having no relation with the taking of food. The fact that the hydrochloric acid of the stomach is diminished in pellagra is used as an argument that the sensation of burning in the stomach and esophagus is of purely nervous origin. Procopiu agrees in this view or thinks that if not due to the nervous influence it is brought about by a lesion of the mucosa of the part which is analogous to the erythema. It is said that sitophobia

occurs frequently in pellagra, among the insane patients especially, but those who are mentally sound often manifest a great disgust for food, especially the meat foods and, according to Marie, polenta. Many patients have an inordinate appetite and will devour everything within their reach regardless of amount or kind. I have seen this symptom in its most exaggerated form, and again, I have seen patients starve themselves owing to the great disgust for any form of food. Marie [1] mentions the case of a pellagrous woman who exhibited this voracious appetite and who just before the onset of the terminal delirium left her house to avoid devouring her children.

Lombroso, Filippi, and Roncoroni made gastric analyses of two pellagrins. The stomach was found practically empty, the first four hours after taking food and the second about two hours. The test meal consisted of a bowl of soup, eighty-five grams of meat, two hundred grams of bread, and one hundred grams of wine. Four tests were made in each case. Hydrochloric was found diminished and lactic acid frequently present.

W. O. Nesbit [2] in a routine examination of the stomach contents of ten pellagrins found the following:

In six cases there was a marked diminution in the acid factors of the gastric juice in the late stages of the disease.

In five cases there was found an excess of mucus during the pellagrous periods.

Six cases showed normal motility, while in three the test was not made.

Four cases showed the presence of bile during severe vomiting periods.

Niles [3] in two hundred cases was able to find records of less than twenty cases in which vomiting occurred and concluded that it was rather an unusual condition.

J. J. Watson writing of the gastric manifestations noted by him said:

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[1] Lavinder and Babcock's translation of Marie's work.
[2] Nesbit, W. O., Trans. Nat. Pel. Cong., 1910.
[3] Niles, G. M., "Pellagra: An American Problem," 1912.

"Vomiting occasionally occurs, but is not a constant feature of the disease. When the disease is advanced dysphagia is complained of by some patients, and this may be accompanied by strangling when fluids are taken.

"Marked gastric symptoms are in evidence in some cases. I have known a case of pellagra diagnosed as gastric cancer. The only abnormality detected by abdominal section was an excessive redness of the peritoneal coat of the stomach. After a few days the patient was rolled out into the sun and soon there appeared on her forehead and hands an intense erythema. This aroused suspicion, and two competent consultants were called in. From the history of repeated attacks of eruption and the picture presented by the patient, the diagnosis of pellagra was made and the subsequent course of the eruption (color, etc.), tongue, diarrhea and depression, put the diagnosis beyond doubt. Hematemesis is sometimes seen."

In a case of my own which will be detailed in the next chapter there occurred persistent vomiting, and the patient gave a history of having vomited half a pint of bright red blood with an absence of any other symptom of gastric ulcer. It should be said, however, that this patient was an alcoholic and there were other symptoms which suggested the probability of cirrhosis of the liver. In other cases I have noted persistent nausea and vomiting, but the percentage in my series of this condition was little more than two per cent so that I must agree with Niles that vomiting in pellagra is not a common symptom.

The changes found in the stomach by Harris were dilatation of the walls in consequence of atrophy of the muscular coat. The mucosa was often pale. In some instances the surface in the pyloric region was quite red.

It would be expected from the pathologic condition that there would be some catarrhal symptoms. Agostini, who studied the stomach very carefully, said that the marked "hypopepsy" which he found was due to a catarrhal condition. He also noted that motor and glandular insufficiency was well marked. It was

further noted that in severe cases the deficiency in hydrochloric acid was more marked than in the mild cases and that in some cases it was entirely absent. As a natural result digestion was found to be greatly impaired, peptones were found deficient, and the catarrhal discharge facilitated the lactic and other fermentations. Allbutt thought that to expect a means of diagnosis from analysis of the stomach contents would not be in order because by the time these changes had existed long enough to assume any definite character other more positive symptoms would have appeared to make the diagnosis a matter of no difficulty.

In describing psilosis pigmentosa C. G. Manning speaks of the occurrence of light red petechiæ scattered throughout the wall of the stomach. He says that these petechiæ are the cause of the blood-stained vomitus and the melena; that there occurs a slow but steady depletion from the intestinal tract as in ankylostomiasis. The petechiæ may be stellate from the presence of congested vessels leading to them. There can be no reasonable doubt that this disease, as mentioned on a previous page, is pellagra, but no other observer has described this condition. It would be a solution of the problem of how gastric hemorrhage can occur, as it certainly does in some cases, without other evidence of definite ulceration.

In the series of one hundred cases reported by the State Board of Health of Illinois fifteen of the number had no diarrhea. This percentage is much higher than in the cases under my observation. This is probably another of the instances in which the disease is seen to vary with the locality. The same thing was illustrated in the consideration of stomatitis, in which instance it was seen that stomatitis did not occur in such a large percentage of the cases in Illinois as in the South. In my own experience there were a few instances of obstipation in place of the usual diarrhea, but such instances were isolated. It is very unusual that some time in the course of the disease this important symptom does not occur.

Tuczek found in the intestinal tract attenuation of the wall in consequence of atrophy of the muscular coat, and hyperemia and ulceration of the lower portion of the large intestine. The ulcera-

tion of the rectum, according to Marie,[1] has been unduly emphasized. Marie noted twice out of seventy autopsies anemia or hyperemia of the gastric and intestinal mucosa. He also noted chronic enteritis with or without cicatrical constriction, thickening of Peyer's patches, and cystic degeneration of the submucous glands.

Out of five autopsies Bardin of Petersburg, Virginia, found three with tubercular lesions of the intestines. This is a matter of importance for the reason that all other sources of diarrhea and hemorrhage must be eliminated before we will be able to draw any definite conclusions regarding the rôle played by pellagra in the causation of these symptoms.

Niles[2] records the findings of E. C. Thrash in two autopsies on victims of pellagra in which the conditions were a departure from the usual. There was practically no change in the intestinal mucosa except a decided thickening in certain parts. This thickening was due to an infiltration of fibrous tissue and the musculature had almost entirely disappeared. The changes in the mucosa were those of chronic inflammation which was characterized by atrophy and disappearance of some of the columnar cells, infiltration of the connective tissue stroma, and foci of amyloid infiltration in the stroma. It could not be said whether or not this finding was peculiar to pellagra or was simply a part of a general cachetic condition. It was thought that the pathologic changes of the gastrointestinal tract were due to an effort on the part of nature to throw off certain poisons which resulted from perverted metabolism and atrophic changes of all the cell structures of the body.

Harris[3] also found atrophy of the muscular coat of the intestine. Anemia and hyperemia he found to be more frequent in the jejunum and he mentions the liability to the formation of ulcers in this same situation but still more so in the ilium. Similar changes were found in the colon. Not infrequently he found the walls of the intestine thinned, but this lesion must not be con-

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[1] Marie, A., "La Pellagra."
[2] Niles, G. M., "Pellagra: An American Problem," 1912.
[3] Harris, H. F., Trans. Nat. Pel. Cong., 1910.

sidered constant as was claimed by the Italian Labus in 1846. This claim was contradicted by Morelli and also by a commission appointed by the Congress of Geneva in 1847 with the result that it was concluded that this condition was inconstant and not to be counted as characteristic of the disease.

The most important post mortem work yet done in this country on pellagra was that of the Illinois State Board of Health. A summary of this work is as follows: [1]

"We have records of eighteen autopsies which were usually made about twenty-four hours after death. A summary of the findings is given in Table No. 3; almost all the patients were senile and one-half of them showed serious concurrent diseases. The only organ which presented striking and constant lesions was the colon. In two-thirds of the cases well-marked ulcers were found, and from the findings in the stools before death and an examination of sections in several cases, most of these may be put down as amebic ulcerations. The ulcers were widely distributed, deep, and undermined, and gave the surface a 'geographical' or 'moth-eaten' appearance. The wall of the colon was considerably thickened and contracted in places. In one case perforation of an ulcer occurred giving rise to an acute peritonitis. In this connection it is significant that Neusser speaks of old and recent ulcers as a finding in pellagra and another author gives perforation as an occasional cause of death. In the remaining cases a well-marked folliculitis was present and in several of these the follicles were the large pre-ulcerative ones found in amebic colitis. The lower end of the ilium also frequently showed folliculitis.

"The condition of the colon was such as to arrest one's attention and an effort was made to find out how long it had prevailed. Autopsy records are available for the past two years. In most cases the intestines were not examined. In twelve cases they were opened, however, and in eight of these particular mention is made of definite ulcerations. One case of multiple abscess of the liver

[1] Bulletin of the Ill. State Bd. of Health, Oct., 1909.

occurred in a case with ulcerations. These facts speak for themselves."

It was found in this Illinois investigation that the patients in general showed as much protozoal infection as did soldiers under field conditions in the Philippines, while the pellagrous patients showed a much larger percentage of infection. The writer aptly says:

"These findings are confusing in endeavoring to estimate the status of diarrhea as an essential symptom of pellagra. The few cases in which no protozoa were found had practically no intestinal disorder, while the remaining cases, showing every gradation of disturbance, from a mild diarrhea to a marked and typical dysentery, had protozoal infections which could, in part, explain the local symptoms. The possible bearing of the findings of examinations of feces on the prevalence of pellagra, will be considered under a discussion of epidemiology."

Many students of the pellagra situation in the United States have been impressed with the rather remarkable prevalence of amebiasis among the victims. Reference has been made in another place to the observations of William Allen in North Carolina on this condition and his conclusion will be found to be in accord with the Illinois results. Until more work is done along the line of a differentiation of the disease-producing amebæ from the non-pathogenic few conclusions can be drawn.

The time of the appearance of the diarrhea in pellagra is variable though it is usual for it to occur with the erythema and stomatitis. It is remarkable how often these three symptoms appear at practically the same time, and it is often difficult to gather from the patient just when it did appear in relation to the time of the appearance of the other two symptoms.

I have observed the most obstinate constipation in pellagra. Its occurrence is a rarity and when found (except in otherwise typical cases) always throws a damper on the diagnosis. Roussel

found that it was not altogether infrequent, especially in the early stages. It often alternates with diarrhea.

Strombio, the elder, distinguished the dysenteric type of diarrhea which was characterized by frequent muco-sanguinolent stools and colicy pain and which was often seen in the early stages; the other type was the ordinary form of diarrhea so well known to all who have seen any of the disease, which is characterized by frequent watery stools, and which cannot be checked. It is a notable fact that this diarrhea will resist even large doses of opium and never ceases under any form of treatment until the disease abates. While the dysenteric type is more frequent in the early stages, the serous diarrhea belongs to the later stages and is said by Marie to be an important factor in producing the characteristic cachexia. It has been stated that there is a peculiar odor to the stools in pellagra, and certain writers think that in some cases a diagnosis may be made from this alone. I have often been forced to endure this odor and I think in some instances it may be characteristic, but it is as unsafe to rely on it as it is to rely on the characteristic odor of typhoid fever. The course of this diarrhea is very protracted, and it is the rule for it to last throughout the whole duration of the disease. Soon after its onset the patient loses sphincter control and it is a frequent sight to find the emaciated victim wearing a diaper in order to protect the bed.

L. B. McBrayer of Asheville, North Carolina, has drawn my attention to the fact that in the mountainous sections the diarrhea is not so frequent as in the low lands, nor is it so intractable when it does occur. This is another proof of the variability of the disease in different sections.

Some of the European pellagrologers have taught that the diarrhea of pellagra is a neurosis and has no organic basis in the intestinal tract; that it is often a symptom of some such condition in the cord as myelitis. All that is necessary to disprove this is to mention the occurrence of fatal intestinal hemorrhage in uncomplicated pellagra. Such a hemorrhage occurred in the experience of J. K. Hall in the State Hospital for the Insane at Morganton, North Carolina. The source of the hemorrhage, of course, was an

extensive ulcer. This occurrence is not at all frequent and must be distinguished from the passages of small amounts of blood so often seen in the dysenteric form of the disease.

It has been stated that pellagra is not a very serious disease among children. There are exceptions to this, but it frequently happens that a child will never see a physician throughout the whole course of the disease. Cachexia is never marked in this class of patient, and as one would naturally expect the diarrhea is very insignificant and never calls for any very active therapeutic measures.

It frequently occurs that incontinence occurs even in the absence of diarrhea. I have seen involuntary movements when the consistency was almost enough to produce definite form.

There are many things about the diarrhea of pellagra which suggest the diarrhea of sprue. The dysenteric symptoms seen in the early stages of pellagra gradually give way to the serous diarrhea; this same thing occurs in sprue. Probably the best means of distinguishing the two conditions is in the character of the stools. The distinguishing feature of the stools in sprue is the yeasty character. The permanence of the looseness of the bowels after the subsidence of active symptoms occurs in both diseases. Long after a case of pellagra is pronounced cured there will remain that tendency for the slightest irritant to produce diarrhea. It would almost seem in some cases that a diarrhea habit had been developed.

The liver is subject to certain changes in pellagra. The organ may be slightly enlarged and friable or it may be decreased in size. Brown atrophy has occurred. Verga reported the occurrence of cirrhosis. By actual weight the liver may be found to be diminished and according to some writers this diminution may reach one-half. Fatty infiltration and sometimes congestion or granulo-fatty degeneration are reported by Marie. Chiarugi in twenty-nine autopsies found nine fatty livers. In five of Harris' autopsies the post mortem weight was only once as much as 1010 grams. He found microscopically the cells of the peripheral portion of the lobules frequently quite fatty, though this change

could not be considered distinctive of pellagra. He found that in some cases the central vein of the lobule was dilated. In the Illinois pellagra report in their eighteen autopsies the liver was fatty in five, in two it was fibrous, in one there were gallstones and adhesions, in one empyema of the gall bladder, in one passive congestion, in one slight cirrhosis, in six it was normal. I have never seen in pellagra symptoms referable to the liver though such a coincidence may occur. So far as I have been able to find in the literature there has never been an instance where the liver produced any definite symptoms.

The pancreas is not affected by pellagra as far as is known at the present time, though Harris refers to a slight atrophy which could be probably accounted for by some other disease process.

CHAPTER VI

NERVOUS AND MENTAL CHANGES IN PELLAGRA

Many of the European pellagrologers have always contended that pellagra should be classified in the group of psycho-neuroses. In a previous chapter an effort has been made to show that it is not a skin disease and has no more right to such a classification than has syphilis. Contrary to the opinion of Strombio, the elder, there is certainly no justification in the classification of it as a gastrointestinal disease. As in Europe the final result of pellagra is invariably a psycho-neurosis, we can readily appreciate the point of view that places the disease in this category. The experience with the disease in the United States demonstrates the insufficiency even of this classification. Probably there has been a greater death rate from pellagra in individuals manifesting no nervous symptoms than otherwise. Such has certainly been my experience and has been borne out by my autopsies. In this chapter I will have little to say about my personal experience with the pathologic changes produced by pellagra, for the reason that my results in the large majority of instances have been negative. The reason for this can be readily appreciated when one remembers that these changes are the result of repeated attacks on the nervous system. It is only rarely that one attack is sufficient to produce demonstrable effects on the nervous tissue. An exception to this rule will be recorded later. Again, it will be stated later that definite psychical disturbances may occur early in the course of the disease without any changes in the brain tissue which could be detected with the most modern methods. It is true that the probable outcome of the ordinary types of pellagra will be insanity, and it is this phase which makes of the disease a great sociological problem.

Up until this time pellagra in this country, as mentioned above, has been either acute or sub-acute in many instances and the victims have succumbed before there was time for the occurrence of any organic lesion of the nervous system. The disease is now assuming rapidly the form seen in Italy, and in another year it seems probable that all differences between the disease on the two continents will have disappeared and there will be a repetition of that peculiar property of diseases so well illustrated in the outbreak of measles in the South Sea Islands. It will be recalled that when this disease first appeared in that country the death rate was over ninety per cent, but now the disease has assumed normal proportions. Just such a thing seems to be occurring in the pellagra situation in the southern states. It will only be a question of time before the insane institutions of the South and possibly of other sections will be shown to be utterly inadequate on account of the great increase in insanity which will be brought about by pellagra. Already in many states there is the great evil of over-crowding. One of the pioneers in the movement for better facilities for the insane is South Carolina, headed by J. W. Babcock, an authority not only on the institutional care of these poor unfortunates, but also on the pellagrous psychoses. This new institution of South Carolina will be built on modern lines throughout, but in addition to the usual meaning of this expression, the pellagrous insane will be provided with accommodations suitable to their particular needs.

There seems no more reason for the classification of pellagra as a nervous disease than for the same classification of syphilis, which also has manifestations in both the skin and nervous system. There are many points of similarity between pellagra and lues, which will be noted later. Until the question of the etiology of pellagra is definitely settled it must remain in an unclassified state. If it were necessary at this time to make an arbitrary classification I would place it in that group of diseases due to an animal parasitic cause, such as syphilis, trypanosomiasis, kala-azar, Rocky Mountain fever, and malaria. The basis for this classification would not be a leaning towards the teaching of

Sambon, but would be due to a belief that a disease of unknown cause had best be classified on a pathologic basis.

Throughout the study of the nervous system of pellagra the student is constantly impressed with the similarity to syphilis. The changes in the tissue at autopsy are very much like the changes of syphilis. In addition to this the seasonal variations, the progressive character of the nervous changes, and the resulting psychical disturbances, as well as many other symptoms which could be mentioned, tend to emphasize this similarity. Tuczek goes so far as to record a condition of dementia paralytica produced by pellagra, though the usually accepted teaching at this time is that syphilis alone causes this mental state.

A comparison from a nervous standpoint of pellagra with ergotism is a matter of considerable interest, especially in the light of the fact that the two diseases have always been linked together in the group of diseases due to grain intoxication; in addition to this there are many points of anatomical similarity which would suggest a connection, though the resemblance is not so marked between pellagra and ergotism as between pellagra and syphilis. That brilliant pellagrologer, F. Tuczek, whose work on the nervous pathology of pellagra is the best on the subject, is outspoken in his declaration of a marked similarity between pellagra and ergotism, based on the following facts which can but impress one with their reasonableness: In both diseases there is an undoubted intoxication process and, preceding the nervous and skin manifestations in both, there is almost invariably a disturbance of the whole gastrointestinal tract. Following a prolonged chronic course in both diseases, cachexia closes the scene. The character of the psychosis, especially that stuporous form of melancholia, is alike in both conditions. In both there occur disturbances of the sensory, the motor, and the vasomotor systems. In ergotism there is a marked tendency for the involvement of the spinal cord to affect the posterior columns, while in pellagra it is the lateral columns which are more usually the seat of the degenerative process. In my own series there was a peculiar frequency of involvement of the posterior columns, and some of

my best pathologic specimens illustrate this occurrence. In ergotism the posterior roots are degenerated and also the column of Burdach in the cord. The column of Goll is said not to be primarily affected but may be involved secondarily in advanced cases (Adami).[1] In addition to this, the anterior root zone, the median portion of the middle zone, and Lissauer's tract escape in ergotism. The posterior roots are not involved in pellagra, and for this reason Marie regards it as an endogenous disease of the spinal cord. This failure of the involvement of the posterior roots when the posterior columns are the seat of a definite degenerative process is very characteristic of pellagra and is shown in the microphotographs.

It will be noted in ergot poisoning that the initial symptoms distinguish it as an acute gastrointestinal intoxication process having its point of attack in the digestive tract. Later on its chief manifestation is as a vaso-constrictor, and this seems to be the predominant action of the poison throughout. There is a rise of blood pressure, and the vessels primarily or secondarily undergo a hyaline degeneration which is shown chiefly in the tunica intima. The local manifestations of gangrene are more or less the result of this constrictor process. In pellagra it will be noted that the blood pressure is lowered throughout and there can be no connection between the erythema and any circulatory disturbance as there is between the gangrene of ergot and the vaso-constriction.

Medical students are taught there are two nervous diseases which do not follow any of the rules of classification; that in these two conditions symptoms occur which are found in many other diseases, but there may be a great combination of such symptoms, making the disease appear as a hybrid, but usually lacking the pathognomonic symptom of any one. These two diseases are syphilis and hysteria. The latter will explain itself in time, as it is a functional disturbance, but the former offers more difficulties. A third disease which offers the same difficulties in pellagrous localities is pellagra. When the patient is seen for the

[1] Adami, G. J., "Pathology," 1911.

first time between the attacks of erythema and when the pre-existing erythema had been very slight, often not impressing the patient or the family as a matter of any note, there is a condition to be reckoned with which may often be classified either as hysteria or syphilis. It is true that the Wasserman and Noguchi tests form valuable adjuncts in avoiding an error, but again a difficulty arises in the fact that some observers find a positive reaction in the Wasserman test in pellagra, though it is counted fainter than in syphilis. It is a daily problem with me and my colleagues to differentiate between myelitis of specific origin and similar pathologic conditions produced by pellagra. Recently, a patient under my care in the James Walker Memorial Hospital in Wilmington, North Carolina, who was familiar with the symptomatology of pellagra because a member of his family had been a victim of the disease, gave us a good history of the malady in order to throw us off the scent of the real disorder. He claimed to have had an erythema of the face and hands and really presented some spurious traces of a skin lesion. His reflexes were all abolished, tactile and temperature sense much perverted, and he had incontinence of the bowel and bladder with trophic disturbances. Very tearfully he denied syphilis, and in the light of his history and the presence of a stomatitis and intestinal disturbances a tentative diagnosis of pellagra was made, pending a Noguchi test. The result of this examination was a very positive reaction.

The pathologic changes which occur in the nervous system in pellagra are of great interest and importance. Tuczek spoke of these changes as heterogeneous. The pigmentation which occurs especially in the ganglion cells is also found normally in old age. Hyperemia, anemia, and edema of the central nervous system and its coverings cannot be counted as distinctive of pellagra. The same thing occurs in a number of other conditions, as chronic spinal and cerebral pachymeningitis and leptomeningitis and spinal arachinitis. The obliteration of the central canal of the cord occurs in many chronic affections of the central nervous system. The findings in the brain in pellagra are usually negative

apart from the occasional occurrence of fatty degeneration or calcification of the intima of the small blood vessels and pigmentation of the adventitial coats. In long-continued psychoses resulting in high degrees of imbecility, atrophy of the cerebrum, chiefly of the cortical substance, is said to occur. The essential changes are to be found in the spinal cord. Tuczek mentions the abnormally rich pigmentation of the nerve cells in the cord as well as in the spinal and sympathetic ganglia, which is frequently

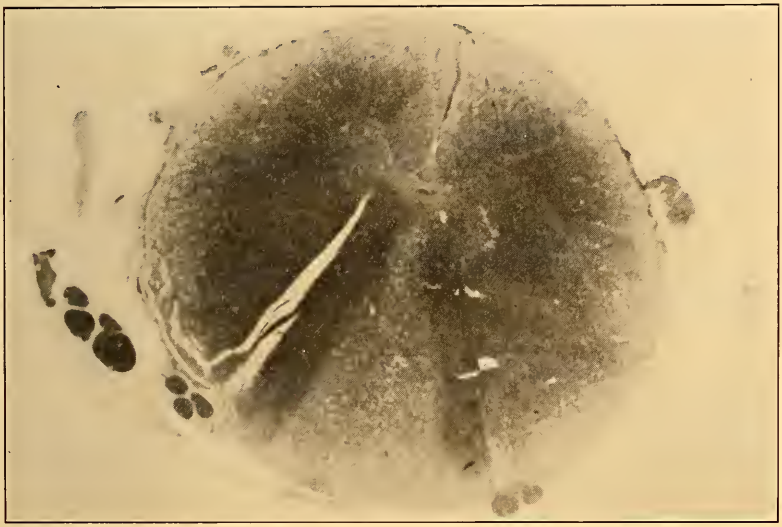

Fig. 29 (*a*). — Upper Dorsal Cord of 17-year-old Girl. (Case of Dr. R. H. Bellamy. Preparation of Dr. H. A. Cotton.)

called pigment atrophy, though such an interpretation of the condition is an error. Bouchard compares the findings in the cord to the pathologic anatomy of tabes dorsalis.

The location of the areas of degeneration in the spinal cord are clearly indicated by the type of the nervous symptoms. As above mentioned, the posterior columns are sometimes involved, though probably not so frequently as the lateral tracts. When the posterior columns are affected the median portions are more often degenerated, but the posterior root zones are never affected. The brunt of the process falls on the crossed pyramidal tracts. The direct cere-

bellar tracts are not involved. The cells of the anterior horns are usually decidedly pigmented. In the late stages muscular atrophy of a general character occurs, but it selects no particular portion of the body. The lesions of the posterior columns occur chiefly in the cervical and upper dorsal regions. The microphotographs

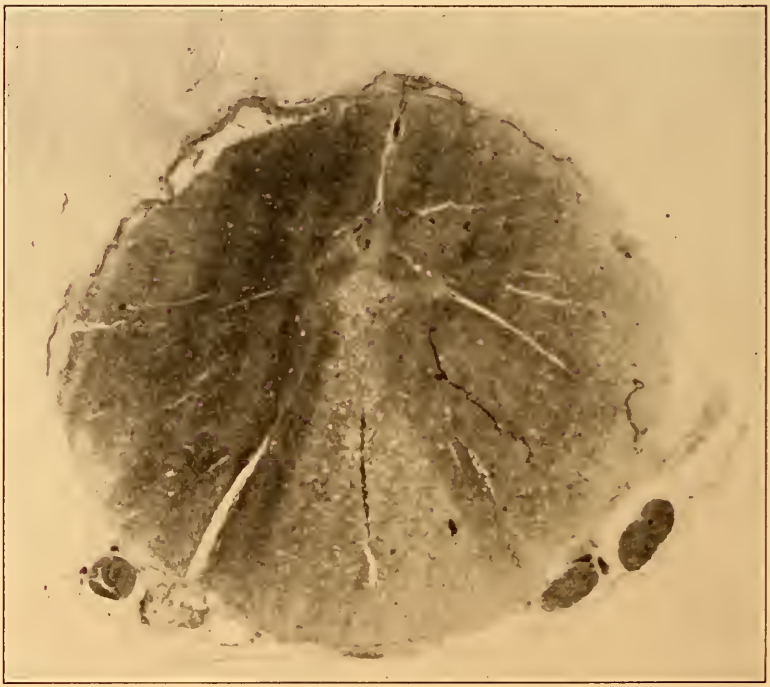

Fig. 29 (*b*). — Mid-dorsal Cord of 17-year-old Girl. (Case of Dr. R. H. Bellamy. Preparation of Dr. H. A. Cotton.)

show a cord with the posterior columns affected. The affection was chiefly in the dorsal segment, the cervical and lumbar segments being only slightly involved. The patient was a negro girl of seventeen years whom I saw through the courtesy of my colleague, R. H. Bellamy. It is a remarkable case, for the reason that the patient died in the first attack, and in our experience it has been the rule that definite organic changes do not occur until after the existence of the disease for at least three years. In this

case the disease appeared early in May, 1909. The first symptom was stomatitis, which was soon followed by diarrhea and later by the characteristic erythema which the patient mistook for sunburn. The erythema was confined to the dorsal surfaces of the hands and forearms, the under surface of each elbow, and small

Fig. 29 (c). — Microphotograph of the Lower Dorsal Cord of 17-year-old Negro Girl. (Case of Dr. R. H. Bellamy. Preparation of Dr. H. A. Cotton.)

areas beneath each knee. In all instances the symmetry was perfect. She was first seen on June 12, 1909. At that time she had been suffering for a week with severe pains in the lumbar region, which radiated into each hip posteriorly. During the preceding twenty-four hours she had lost the use of the lower limbs. On July 7 the systolic blood pressure was 110. She complained of burning and tingling pain from the crest of the ilia downward, involving the upper one-fifth of the thighs. Pre-

viously in this area there had been a loss of tactile sense, but at this time there was a return of this sense. She was also able to move the thighs, but it was done by the psoas and quadratus muscles and the movement was very slight. This had not been

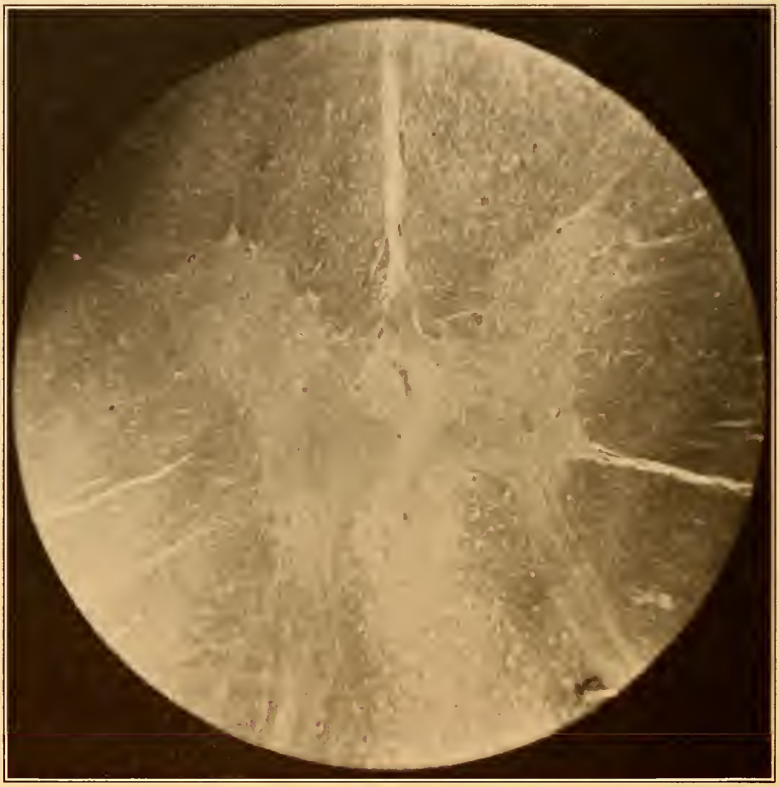

Fig. 29 (*d*). — Microphotograph of the Dorsal Cord of 17-year-old Girl (Negro). (Case of Dr. R. H. Bellamy. Preparation of Dr. H. A. Cotton.)

possible at the previous examinations, as these muscles too had shared in the general process of paresis. On July 12 it was noted in Doctor Bellamy's record that the areas of anesthesia were about the same and there was no change in the motor condition; diarrhea was more aggravated and emaciation was extreme. In spite of good attention bed sores developed. On July 17 tactile

sense was found to be improving. The areas in which sensation had returned extended to the junction of the middle and upper thirds of the thigh. In these areas of returning sensation the patient complained of burning pain. She was nauseated and very irritable and the volume of the pulse was poor. There was a decided disturbance of temperature sense and total motor paralysis, together with inability to void the urine. She was catheterized without experiencing any sensation of the operation. The temperature was 101° F. and the pulse 100. On July 18 there was little change except that the power to appreciate a full bladder and ability to void the urine had returned. The temperature at this time was 101.4° F. and pulse 110. Her clouded mentality was improving. The stomatitis was less, but the diarrhea persistent. On July 23 the erythema was rapidly subsiding and there was an improvement in the mouth and intestinal symptoms. The nervous condition was practically unchanged. The motor paralysis from the crests of the ilia downward was complete. July 28. No change in the nervous system. The feet were quite edematous. Temperature was 100° F. and pulse 96, being of good volume. The patient seemed to be stuporous, and it was necessary to arouse her in order to question her; throughout the examination she remained in this state. The heart and lungs were negative and the abdomen also, except for a tender area in the epigastrium. The pupils were equal and responded both to light and accommodation. The blood showed a secondary anemia of moderate degree and no leucocytosis. The urine was negative. There was total motor and sensory paralysis of the lower extremities and an absence of all reflexes. On August 7 she was vomiting, her feet were very edematous, and the pulse was of poor volume. She was able to move the toes very slightly. The reflexes were absent. On August 14 the anesthesia had disappeared from the toes to the knees and the sensation of burning and tingling had returned. She was able to move her toes fairly well. Enormous bed sores had developed. The temperature was 100° F. and the pulse 120.

A few days after this last observation the patient died during

a spell of very hot weather. Her home was in an isolated place many miles from us, and the autopsy was unavoidably delayed, and when done could be only partial owing to the fact that the negroes were threatening us and we were forced to work very hurriedly. Consequently we were very glad to escape with our lives and the spinal cord in a solution of formalin. H. A. Cotton of the State Hospital for the Insane of New Jersey at Trenton kindly prepared the material. On holding these preparations up to the light one would suspect at once that the lesion was that of locomotor ataxia, but, as mentioned in pellagra, the posterior roots are not involved in the degenerative process as in the former disease.

Tuczek[1] made exhaustive studies of eight cases of pellagra, and his findings are of great interest and importance. Seven of these eight cases showed degeneration of the posterior columns of the cord. In one it was limited to Goll's column and a medial strip of Burdach's. In five cases it extended throughout the whole length of the cord. In one case the involvement was confined to the cervical segment. In four the dorsal region was the chief seat of degeneration. In five cases the crossed pyramidal tract was affected. In the first the affected areas extended from the upper cervical to the upper dorsal with degeneration of the cells in the anterior and posterior horns in the middle and lower cervical regions; in the upper dorsal region there was found atrophy of the cells in the anterior horns and the column of Clark, as well as atrophy of the anterior root fibers. In the second the degeneration of the crossed pyramidal tracts was more intense in the dorsal region, but extended as high upward as the middle cervical and as low as the upper dorsal regions. In the third case the lesion extended throughout the cord, but was more marked in the dorsal portion. In the fourth case the lesion was confined to the dorsal portion. In the fifth the degeneration was massive and limited to the middle cervical region.

In one of Tuczek's cases in the middle cervical region the

[1] Tuczek, F., "Klin. u. anatom. Studien ueber die Pellagra." 1893.

left anterior horn was constricted to the point of complete separation; the posterior columns formed an angle with each other; the anterior fissure was displaced and removed through the white commissure. The central canal of the cord is often dislocated and in one instance it was doubled. Clark's column may be displaced, and in one instance in the upper portion of the cord it was drawn to the right and in the lower portion to the left, but the elements of the columns were normal. The central canal is liable to be obliterated at any level. Corpora amylacea were abundant in the region of the central canal and entered the posterior roots as well as the septum posticum in the posterior horns and in Goll's column. The posterior columns may be the situation of a bilateral symmetrical degeneration, which is indicated by an atrophy of nerve fibers and an increase in the size of the interstices. The ganglion cells are found to be rich in pigment and in the affected areas there is a degeneration or absence of nuclei and processes. In some instances there occurred small masses of pigment drawn together, while in others the nuclei were scarcely visible. Occasionally vacuolation was found. The chief seat of the degenerated atrophic ganglion cells was in the periphery of the cortex. The fine net-like fibers were found to be richly developed in the cortical region of the anterior horns. In one instance there was found in the center of the anterior horn in the lower cervical region a small polio-myelitic focus. In the lumbar cord throughout the whole medullary sheath were found large spindle cells, which may occur in all tracts. The pia mater showed no alterations and nothing abnormal was noted, as a rule, in the blood vessels. In the degenerated postero-lateral tracts there was noted in one case a slight increase in the nuclei. The anterior roots of the spinal nerves may be atrophied. Glia cells in the anterior horns are sometimes rich in pigment. The coverings of the cord, as previously mentioned, are invariably normal. Körnchen cells are found exclusively in the postero-lateral tracts. The diseased tracts present a uniform sclerosis with atrophy of nerve fibers, separation of the interstices, and striking nuclear increase. Changes in the central canal of the cord often suggest

syringo-myelia, and it is further difficult in many cases to explain the trophic and anesthetic symptoms by the skin changes.

Mariani's finding of constant arterio-sclerosis is not borne out generally by other observers. Extension of the perivascular spaces may occur in the cord as well as in the cerebral cortex.

The glia tissue of the commissure is often much increased, and this fact is confirmed by Golgi, Tuczek, Lukacs, and Fabinyi. The last two of these observers found extreme extension of the perivascular space of all three of the central arteries and thought that it was directly related to the occurrence of the pellagrous process. These same observers found that disintegration of the sheath of the spinal cord was nowhere complete, but was most decided in the region of the cervical vertebræ. They thought that in all probability this was related to the fact that beginning at this point and continuing downwards many cells of the posterior cornua were degenerated. This was confirmatory of the view of Babes, who thought that the disintegration of the sheath was of endogenous origin. The gray degeneration of the column of Goll was found to be especially frequent in pellagra. Tuczek and Marie stated that this process, combined with degeneration of the lateral tracts, presented a characteristic of a systemic disease. Lukacs and Fabinyi,[1] however, were inclined to the view of Babes, which attributed the degeneration of the spinal cord to a selective process caused by the degeneration of the ganglia, or, possibly also, to the endogenous result of the disappearance of the cells of the posterior cornua. The fact that many fibers remain uninjured favors this view. These observers differentiate the disease of the cord in pellagra from tabes dorsalis by the fact that the degeneration in the former is confined to the cervical cord (Belmondo) and by the lack of any involvement of Lissauer's tract. They also found the cells of Clark's column degenerated to a marked degree. The above-mentioned view of Belmondo regarding the limitation of the degenerative process to the cervical portion of the cord is not invariable. It may be said,

[1] Lukacs and Fabinyi, "Allgemeine Zeitschrift fuer Psychiatrie." Vol. LXV, Part 4. Aug. 29, 1908.

however, that locomotor ataxia does cause more pathologic changes in the dorsal and lumbar cord than does pellagra.

The sensory cells of the posterior cornua show less changes than the badly diseased cells of the anterior cornua, which are affected in the cervical region. The column of Clark is especially affected and the cells show a homogeneous swelling with nucleolysis and chromatolysis and the remains of the chromatin form a wreath at the circumference. Katonsky noted a granular condition of the glia cells. In cachectic cases melanosis is frequent, and this resulted in the conclusion of Tinotti and Tedeshi that the condition is allied to Addison's disease. Babes found the lesions of the cord closely resembling those of tabes, such as degeneration of the posterior roots of the spinal nerves and the posterior columns. It was also found that those lesions were more frequent in the cervical segment. In the chronic form of the disease running a very close course the anatomico-pathological alterations are very similar to those of progressive paralysis and tabes dorsalis. In 1899 Babes and Sion made a valuable contribution to the study of the neuro-pathology of pellagra. They found in the nerve cells, especially the large chromophilic cells of the cortex, signs of unquestionable degenerative changes. The tigroid bodies lost the power of staining with the basic dyes and the cells became swollen and vacuolated. The nuclei were pushed aside and lost the power of taking the basic stains and presented swollen nucleoli; the pigment in these cells was also dislocated, and instead of being around the nucleus lay scattered throughout the cell body. The processes of the cell appeared to be broken off and seemed swollen. The perivascular lymph spaces were dilated and the walls of these cavities were frequently lined with yellow pigment. In the brain tissue small collections of lymphoid cells were frequently encountered and the neuroglia cells in the vicinity of the blood vessels were swollen. These alterations have been in the main confirmed by Marinesco, Rossi, Richette and Grimaldi, and Harris [1] in this country. The last-mentioned observer adds that the small vessels of the brain seemed unusually filled with

[1] Harris, H. F., Trans. Nat. Pel. Cong., 1910.

blood and the perivascular lymph spaces quite uniformly dilated. There were no collections of lymphoid cells anywhere in the tissues. The nerve cells showing degenerative changes usually measured less than the normal cells and always contained a greater or less amount of acidophilic protoplasm. He found that the cells in different portions of the brain suffered in varying degree. Perhon and Papinian, according to Harris, have demonstrated, as would be expected, that the neuro-fibrils of the cells show degenerative changes. Alterations similar to those found in the cerebrum have been observed by Harris in the nerve cells of Purkinje. The cell protoplasm was found to lose its affinity for basic stains, and the nuclei underwent a similar change. Harris states that the nerve cells showed every stage of degeneration from slight loss of chromophilic substance to practical destruction of the cell body. He found the changes in the cord to be confined chiefly to the lower cervical and dorsal segments.

It is interesting at this point to note the distinction drawn by Lombroso between pellagra and tabes dorsalis. He said that in most instances typical cases suggested locomotor ataxia in its incipiency, with the differences that in pellagra few changes were found below the dorsal region, while in tabes the lumbar region is chiefly affected, though the cervical segment may be most involved. Both diseases, he said, show degenerative changes in different portions of the spinal cord, while tabes attacked the posterior columns especially and pellagra the lateral or both posterior and lateral. Both diseases presented the picture of a combination sclerosis. Marie thought that the sclerosis of pellagra resembled more closely that of general paresis than tabes. It was further noted that edema of the central nervous system and a chronic leptomeningitis is common to general paresis and pellagra. Rohrer's [1] view of the pathology of pellagra is that it should be classified with the infective granulomata. He says that the small tumor-like nodules or granulomata are seen to be composed of a necrotic center surrounded by spindle-shaped cells and small round cells, very similar to tubercles or gummata with-

[1] Rohrer, C. W. G., Trans. Nat. Pellagra Cong., 1909, p. 145 *et seq.*

out giant cells. These granulomata he found most abundent in the walls of the superficial blood vessels of the lungs, but especially the upper lobe of the right lung. After the lung, in order of abundance, were the superficial blood vessels of the brain, which, he claimed, furnished a pathologic basis for the distressing mental symptoms which were apparent in the last stage of the disease.

Randolph and Green [1] mentioned the finding of a glistening dura, a thickened pia, and small hard plaques in the arachnoid, which was also noted by Lombroso.

Marie [2] found opacity of the pia mater and thickening of the pia and arachnoid, which in some instances was circumscribed but more often diffuse. This condition occurred with a purulent exudate or with hemorrhagic extravasation under the arachnoid. In some instances there was found extensive or partial edema of the brain, to which was often added edematous softening around the pillars of the fornix or at the foot of the hippocampus. Five times in one hundred and thirteen autopsies was found hardening of the cerebellum, while in eight cases of the same series it was soft and edematous. In eleven instances there was atrophy of the brain, especially in the cortical substance. In eighteen out of twenty-eight cases examined the weight of the brain was diminished, while in seven it was increased above normal. In five instances hyperemia of the brain was noted, twice of the corpus striatum, in one more marked on the right than the left. In four cases there was anemia of the brain. Marie [2] recorded the following findings from the literature:

Nardi, Fanzago, and Strombio reported injection of the membranes with thickening of the arachnoid and congestion of the sinuses. In most of his autopsies Liberali found inflammatory changes in the arachnoid. In twenty-one out of forty-one cases Verga found adhesions of the dura mater to the superior cranial bones; twice thickening of the dura mater; three times opacities

[1] Randolph and Green, *Ibid.*

[2] Marie, A., "La Pellagra," and authorized translation with notes by Lavinder and Babcock.

of the arachnoid; and in one case only was there adhesions of the pia mater. In sixteen autopsies Rizzi found the pia involved in every instance. Morelli found extravasations of blood beneath the meninges very frequently. Verga in eight cases found hydrops of the ventricles and four times softening of the cerebral substance. Microscopic examination showed in eleven instances a fatty or pigmentary degeneration; in four cases the two were combined in the walls of the cerebral capillaries; three cases with calcareous degeneration; one instance of sclerotic changes in the brain; one case of dilatation of the capillaries of the brain. Out of twelve examinations of the sympathetic ganglia, decided pigmentation of the ganglion cells was found in eight instances.

Leonardo Bianchi [1] said:

". . . I must make special mention of the alterations of the abdominal sympathetic system (Babes and Fox), and the parenchymatous neuritis found by Dejerine. In the brain we find thickening, turbidity, and often adhesions of the meninges, atrophy and induration of the cerebral substance, increase of the subarachnoid fluid, profound alteration of the cerebral cells, and increase of the neuroglia. In the acute cases the usual cell alterations are those found in other acute forms of psychosis. In the spinal medulla lesions are found in the various bundles (Tonnini), just as in progressive paralysis. In one case the pyramidal bundles are most affected, in another the sensory bundles, in a third the central substance."

Tuczek's findings in the cells of the central nervous system were essentially the changes of parenchymatous nature. The chromatolysis was advanced even to the point of destruction of the chromatophilic substance, together with swelling, vacuolization, and nucleo-atrophy. These changes were chiefly of the nerve cells of the cerebrum and especially of the paracentral gyrus,

[1] Bianchi, Leonardo: "Pellagrous Insanity" in "Textbook of Psychiatry," translated by J. H. Macdonald. 1906.

of the medulla oblongata, and of the cord. In one of his cases with the symptom complex of progressive paralysis he found a breaking up of the medullated fibers of the cerebrum just as typically occurs in dementia paralytica. In the discussion of a paper read by me [1] before the College of Physicians of Philadelphia recently, H. A. Cotton mentioned a class of cases described by Adolph Meyer under the name "central neuritis" and thought that the mental symptoms presented by some of my cases strongly suggested this condition. This idea is strongly borne out by the statement of Siler who thinks that pellagra occurs in practically all the insane institutions in the United States. Cotton mentioned the occurrence in these cases of stupor or anxious delirium together with rigidity, peculiar muscular spasms or jactitations, and obstinate diarrhea. All of the cases observed by him ended fatally. He said that the etiology of central neuritis was obscure, but it was undoubtedly due to an intoxication. The histo-pathology has been definitely described and can be easily diagnosed by a competent neuro-pathologist. While the two diseases cannot be counted altogether similar, still they probably arose from the same pathological process. Soon after this I sent a brain and cord from a rather atypical case of pellagra to Doctor Cotton for a further investigation of this interesting point. He wrote me in reply:

"My suspicions regarding the similarity of this process with that of central neuritis is well borne out in this case. The large motor cells and a great many cells in other regions show 'axonal reaction' to a very marked degree.

"The condition has been somewhat described by Marinesco and other Italian observers as 'chromatolysis,' but none of them have recognized that it is an 'axonal reaction.' In other words, it is a parenchymatous degeneration of the central nervous system."

A marked similarity will be found in this description and that of Tuczek and others of pellagra. The matter certainly deserves

[1] Wood, E. J., "Appearance of Pellagra in the United States." Trans. College of Physicians of Phila. 1909.

further investigation. If a definite pathologic basis can be found, many of the cases of so-called "pellagra-sine-pellagra" can be cleared up and a clinical study of this condition, if such a condition exists, can be made and it can thereby be placed on a more satisfactory footing. It is not at all improbable that many of the cases in our state institutions with the diagnosis of dementia paralytica really belong to the group of pellagra psychoses. Such a possibility has been mentioned on a previous page, and I can state of my own knowledge that such an error is by no means rare in some institutions where the cases are definitely and carefully classified, and such a thing is not at all surprising when such a distinguished neuro-pathologist as well as pellagrologer, as Tuczek should make the statement that he found a definite condition of dementia paralytica in one of his cases of uncomplicated pellagra.

Tuczek emphasizes the fact set forth earlier in this chapter that the nervous disturbances in pellagra remain for a long time on the border line between functional affections and fixed pathologic processes. This is manifested by the occurrence of improvement of symptoms on the one hand and by fixedness on the other. It also is manifested by diffuseness on the one hand and localizing properties on the other. He says that a tendency to progressiveness is a characteristic sign of pellagra. Numerous cases from my records will be introduced to show this point. It will be seen that in many instances from the character of the symptoms one would have good ground to look for definite organic changes in the nervous system, and yet these signs will be wanting at autopsy in spite of the employment of the most improved methods of pathologic technique. One case in particular, studied clinically by me and microscopically by Doctor Cotton, will now be recorded. This case was described in the beginning (December 7, 1907) under the title "A Mixed Infection with Tertian and Quartan Malaria Occurring in a Patient with Symmetrical Gangrene."[1] It was not recognized at that time as a case of pellagra and, as previously stated, I was indebted to Searcy and others

[1] Wood, E. J., *Jour. Am. Med. Assoc.*, XLIX, p. 1891. 1907.

in Alabama for setting me straight in supplying the proper diagnosis. While at work in the laboratory of Alois Alzheimer in Kraeplein's clinic in Munich, Doctor Cotton became interested in my pathologic material which I had with me and since that time has given me the benefit of his skill as a neuro-pathologist.

The patient was a man, aged 46; his occupation was that of a grocer. There was nothing of note in his previous medical history except an absence of syphilis and malaria. He was a remarkably strong, robust man. The beginning of his sickness occurred without any prodrome, with high fever which developed during the night and was followed by a profuse sweat. One week later his wife noticed that he was acting peculiarly. Among the strange things which she noticed was that he would ring his own door bell instead of using his night latch. He seemed to be dazed and was unable to attend to his business, making many absurd mistakes. There were no outbursts and no other mental changes noticed except this dazed condition and a general apathy.

For six months his condition remained unchanged. At this time his mental disturbance became much exaggerated and there was added to the previous symptoms utter indifference to everything. His bowels and bladder would be emptied in bed and the patient was apparently oblivious to his filthy condition. There was marked muscular weakness. Speech was slow and somewhat hesitating. There was some tremor present. The reflexes were rather sluggish. Pupils reacted to light and accommodation. The tests showed an absence of temperature sense and a great impairment of tactile sense. For the greater portion of the time this patient remained quietly in bed. On the back of each hand was an area of exfoliating skin. The two areas were symmetrical in position, shape, and size. The erythematous process was practically over at this time. The patient told me that during the preceding month he had had several chills, for which he was given quinine. This was nine months after the beginning of the affection. About three months later, on October 27, 1905, he was admitted to the James Walker Memorial Hospital in Wilmington, North Carolina. At this time the posterior surfaces

of both hands were affected with a dry exfoliative lesion extending from the tips of the fingers to two inches above the wrist joints and the lines of demarcation were perfectly symmetrical in position and direction (Fig. 23). The finger tips were considerably atrophic, corresponding in this regard to the classical description of Raynand's disease. The lesions were painless. On the external surface of the right leg, involving the lower third of the lower leg and the external surface of the foot, was a large moist ulcerative area penetrating to the muscle (Fig. 22). On the left leg was a much smaller area of the dry exfoliative variety. This leg manifested at times the appearance of a local syncope, becoming cold and apparently bloodless, and again it would become cyanotic. As the chart shows (Chart II) the temperature at this time and for a period certainly of three weeks, never rose above 99.6° F. There was an absence of chills. The heart, lungs, kidneys, and liver were negative on examination. There was a simple secondary anemia and no leucocytosis. There was nothing suggestive of malaria, and yet during these three weeks the blood was loaded with tertian parasites in all stages of development. According to Craig, latent malaria is often characterized by organisms in all stages. Latent malaria in the southern states is practically unknown. In the routine examination of the blood for malarial parasites this is the only case found out of several hundred examinations. In spite of the presence of the parasites in the blood the temperature remained practically normal and the lesions progressed favorably.

On November 29 the temperature rose without any preceding evidence of a chill to 104° F. The blood at this time contained numerous quartan parasites and also some tertian, though the former predominated. The blood was examined every two hours and no quinine was given. Two hours after the rise of temperature the blood contained many large non-pigmented tertian parasites and only a few young quartans. Two hours later both varieties were abundant but the quartan probably predominated. At the next examination, two hours later, the number of tertians was small. The temperature rose three times on consecutive days

and at the time of each rise the quartan parasites predominated; the tertian while present were found in only very small numbers. After the third rise there was an interval of moderate temperature, with a rise on the fourth day to 105° F. Again, on the fifth day, after an interval of irregular temperature, there occurred another rise to 105° F. At this time quinine was given hypodermically with prompt response. This treatment was followed by iron and arsenic. For a period of forty days there was no fever, no skin lesions, and a decided improvement in the mental condition. After this interval of normal and subnormal tempera-

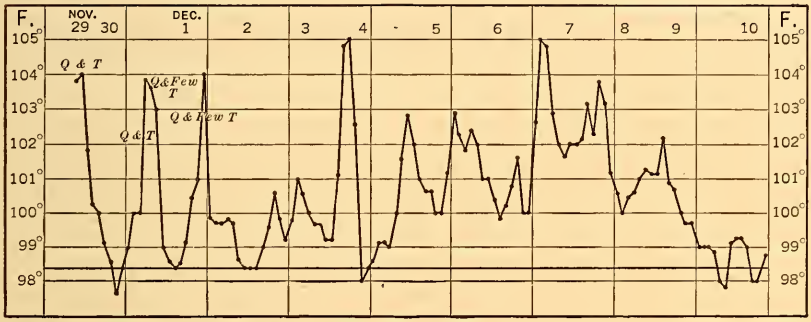

Chart II. — Author's Case. (*Jour. Am. Med. Assoc.*, Vol. XLIX, p. 1891. Trans. College of Physicians of Philadelphia, 1908.) Combination of Tertian and Quartan Malaria in a Pellagrin.

ture a relapse occurred. It was my misfortune to have been away from the city at the time, but I returned in time to secure an autopsy. The idea of a relapse was confirmed, as the vessels of the brain, liver, and spleen were filled with parasites and pigment. I was able to find only the quartan organisms. The specimens were unfortunately preserved in formalin, which interfered seriously with some of the histo-pathologic work which was desired. Doctor Cotton again did the neuro-pathologic work for me and wrote as follows:

"I was able to get a fairly good stain, enough to make a diagnosis, or rather, no diagnosis, as the cortex showed no reaction that could be considered pathologic. The topography was un-

altered and the elements of the cortex were not affected by the malarial infection. There was probably an excess of pigment in the nerve cells, which could be accounted for by the patient's age. The blood vessels appeared a trifle thickened, but the fixed cells did not seem altered or to have proliferated at all and the vessels were not increased in number. There was no evidence of general paralysis or other organic affection and no evidence of cerebral syphilis. The parasites were very easily seen in the blood stream and in great numbers. There was nothing of note in the cord and peripheral nerves."

It is a question as to the origin of this pigment. It seems reasonable that it was due to the pellagra. At the time of this examination it was not known that such a disease as pellagra existed on this continent and none of us were familiar with any phase of it. It seems rather remarkable that there should have been no organic nervous changes in the presence of such definite psychical manifestations and especially as the patient had been sick long enough for an impression to have been made on the nervous tissue. It is interesting to compare this case with the case of the negro girl of 17 years whose cord presented such definite degenerative areas. (See microphotographs and account of this case on page 230 of this chapter.) It has been impressed on me many times that symptoms which to all appearances had a definite organic basis were really nothing more than functional without any definite pathology. This fact is well illustrated in the following case.

Mrs. C. S., aged 33. Mother of three children. No history of miscarriage. Hygienic conditions good. Her family history was negative. Her previous medical history was negative, except for typhoid in childhood.

About ten years ago, two years after her marriage, she began to be troubled with vertigo, fainting, and "a rush of blood to the head." These symptoms kept her in bed for nearly two years. Her physician was unable to find a cause. At this time there were neither intestinal nor skin lesions. She finally improved and was

able to resume her household duties. For at least four years she has suffered every spring with digestive disturbances; everything she ate caused digestive distress which the patient thought was made worse by meat food. Stomatitis was among her many symptoms. She was unable to recall the existence of any erythema until the spring of 1909. (These notes are dated October 13, 1909.) The skin lesions were typical, extending four inches above the wrist and were of the dry variety. She complained of burning of her hands, and in the lower extremities she suffered with itching, stinging, and cutis anserina. Diarrhea was not a very distressing symptom. Her heart and lungs were negative. The systolic blood pressure was 148. All reflexes were greatly exaggerated and there was marked ankle clonus. No nystagmus was present. She was unable to cross her knees without help, suggesting a "lead pipe" condition. The pupils were very active to accommodation and sluggish to light. This sluggishness was more noticeable in the left eye. The patient was given the usual treatment with atoxyl hypodermically, but did not improve. She was very depressed and emotional, unable to stand or even to feed herself. She was so insistent in her demands to go home that she was discharged from the hospital and sent home on a stretcher, as she was practically helpless. I did not hear from her for over a year, when I chanced to meet her physician. Much to my surprise the patient was not dead, but had almost entirely recovered, and the doctor reported that she had resumed her usual household duties and was able to perform any activity that she was ever able to do in the days of good health.

It was reasonable to suppose that a condition of such long duration and with such definite symptoms of cord changes should have an organic basis. The termination naturally suggested a mere functional disturbance.

In the table of the Illinois State Board of Health for October, 1909, which is here reproduced, we find a great diversity of the reflexes indicating a parallel diversity in pathologic conditions. This matter is referred to at this place because of its bearing on the underlying pathology. In 56 per cent there was increase

of the patellar reflex; 35 per cent showed exaggeration of the biceps reflex; 34 per cent with exaggeration of the wrist reflex; 48 per cent with exaggeration of the plantar reflex. In 20 per cent the biceps reflex was decreased, and in 14 per cent the plantar reflex was diminished. The Babinski reflex was present in 13 per cent and absent in 87 per cent. A further study of this table will show such an intricacy of variations that the cases cannot be divided up into two great groups: one with the lesion of the lateral tracts, and the other with the lesion of the posterior tracts. It will be noted in many instances that there is exaggeration of one reflex and decrease of another. In not a single case of this series of one hundred was there an instance with reflexes normal throughout. Since the first two years of my experience with pellagra this has been my experience with a much larger series of cases. As mentioned formerly, in our first experience with this disease, the patient died or recovered before there was time for any indelible impression to be made on the nervous system. Cases will be introduced into the text to illustrate this point. In the majority of cases I have been impressed with the peculiar variations of the reflexes in the same individual. In some instances the reflexes of the upper extremity are exaggerated while the reflexes of the lower extremity are diminished, and the reverse of this. The reflexes of one-half of the body may be exaggerated and of the other half normal or diminished.

The nervous symptoms of pellagra are affected by the seasonal variations, just as are the skin and intestinal manifestations, though not to such a marked degree. With each recurrence the impression on the nervous system is made more permanent until finally there is no further amelioration of symptoms, and it is usually at this point that the line can be drawn between functional and organic lesions. Tuczek noted that the reflexes may be increased up to the point of intense clonic contraction. He also reported clonus of the upper leg with flexion on the hip. In many instances I have found ankle clonus present. In a series of 300 cases Tuczek found half with decided increase of the knee jerk up to rapid patellar clonus, even on the slightest per-

cussion of the tendon. In from 30 to 40 there was dorsal clonus and a decided increase of the tendon reflexes of the upper extremity. In 8 cases the knee jerks were wanting; in the remaining, partly weakened and partly normal. Differences in the activity of the two sides were frequently noted. In recent cases the deviation from normal was greater at the height of the pellagrous outbreak. In none of the cases with no knee jerk was there a trace of ataxia. With an increase in the tendon reflexes there also occurs, in some instances, muscular weakness, contractures, and spastic gait very similar to spastic spinal paralysis. The Babinski reflex was only recently noted in pellagra. It is said that the spinal symptoms are not always progressive and may remain stationary. The triad of symptoms, paresis, spastic appearances, and increase of tendon reflexes, may remain for years without the occurrence of contractures, and according to Tuczek even in case of severe damage to the cord regeneration may take place.

The following fatal case with mental disturbances is recorded to illustrate grave pellagra without any alteration of reflexes.

Mrs. A. R., examined July 15, 1909. Housewife. Fairly well conditioned. Three children living and well. Family and previous medical histories have no bearing on present condition. In June, 1908, she suffered from obstinate diarrhea, which subsided during the following winter, though she did not regain her normal tone. Early in July, 1909, the characteristic erythema appeared on the forearms. Following the erythema of the hands there was bleb formation. Stomatitis appeared with the erythema. She complained of globus hysterica and with a constant disagreeable taste. The lesions later appeared on the back of the neck and the chin. There occurred the vaginitis so commonly observed in pellagra. Soon after there was noted a mental deterioration characterized chiefly by despondency. She complained of pain in the head and eyes, and also of vertigo. The reflexes remained normal and the patient died in September, 1909.

This case cannot be classified with the acute or fulminat-

ing, as she had been affected for a much longer time than is the course of such cases. It seems remarkable that there should not have been some spinal changes indicated by alteration of reflexes.

Mrs. J. P., June 23, 1909. A poorly conditioned woman of the farming class. She has three children and had a miscarriage at six months in her first pregnancy. One month ago she noticed an erythema over the wrist joint, which extended upward and also downward. It involved the whole of the back of the hand and fingers. The upward extension included the point of the elbow. A portion of the forearm lesions were vesicular and in every instance symmetry was well defined. Mouth and lips were quite sore. One month before the appearance of the skin symptom there was noted a profuse diarrhea, which decreased with the appearance of skin lesions. At the time of the examination there was noted fresh symmetrical lesions on both sides of the neck posteriorly and a small area over the upper outer angle of the left eye. The arm lesion was the most extensive I have ever seen, covering the whole of the posterior surface of the forearm and combining the moist and dry varieties. The lips were much inflamed. The tongue and mucous membrane of the whole mouth were red without ulcerated areas. There was some salivation. The reflexes were normal. It was noted that there was present the usual retardation in replying to questions.

Again, in this case, although it was recent, changes in the cord would be expected because of the severity of the symptoms.

Many nervous symptoms have been reported as resulting from the action of the pellagrous poison. Among these are mentioned by Lavinder and Babcock neurasthenia, hypochondria, neuralgia, chorea, sciatica, polyneuritis, meningitis, myelitis, "epilepsy," and "tetanus." Neusser described a case of amyotrophic lateral sclerosis, but such an occurrence must be exceedingly rare, as I can find no other reference in the literature to such a condition. In this connection the following reference of J. W. Mobley [1] is of interest:

[1] Mobley, J. W., Trans. Nat. Pel. Cong., 1910.

"In considering the neuro-psychic phase of pellagra, it will be expedient to study, first, the two conditions together, without attention to their strict division into separate clinical entities. Indeed, I might say, seldom do we have in Georgia an organic disease of the nervous system, of pellagrous origin, without invasion of the psychic realm. On the contrary, so intimately associated are the two maladies in many of their clinical aspects, that we are often perplexed to know which, if either, merits the place of priority in occurrence. An illustration will more adequately explain the confusion which has arisen in the author's mind as to whether a primary neurosis of a non-pellagrous etiology might exhibit a secondary symptom complex, simulating the pellagrous syndrome. Take, for example, amyotrophic lateral sclerosis complicated with insanity, — the two diseases may progress with the preponderance of symptoms favoring a spinal lesion as the primary site of invasion. The mental states may vary from mild confusion to complete delirium; the reflexes may be exaggerated with a variable Babinski and Gordon paradox; the patient gradually develops a sore mouth, with alternating diarrhea and constipation; later the skin lesions appear with variable intensity. Have we pellagra with amyotrophic lateral sclerosis and insanity as complications, or have we insanity and organic cord disease, with a pellagrous complex?"

Bassoe of the Illinois Pellagra Commission in a study of nineteen cases made of them three groups: cases where degeneration of the pyramidal tracts was probable; cases of degeneration of the posterior columns; cases with combined degenerations. These results were confirmed at autopsy in most instances.

In a case of my series symptoms occurred which strongly suggested acute ascending paralysis (Landry). This disease has been known to follow the specific fevers, especially in debilitated patients. It is not uncommon in typhoid fever to have such a sequel. Ross, Neuwerk, Barth,[1] and others claim that it is a peripheral neuritis, while Spiller [1] found in a rapidly fatal case destructive changes in the peripheral nerves and corresponding

[1] Osler, Wm., "Practice of Medicine." 1906.

alterations in the cell bodies of the ventral horns. He thought that some toxic agent acted on the lower motor neurones as a whole and explained the absence of lesions in some cases on the ground that delicate methods were not used in the study. Buzzard found the *Micrococcus thecalis* in pure culture in one case. There are those who claim that the disease is a functional disorder without any anatomical basis. At the present Osler [1] regards the disease as an acute poisoning of the lower motor neurones.

E. H. White, aged 27 years. Observed August 26, 1909, in the James Walker Memorial Hospital, Wilmington, North Carolina. He was a prosperous merchant in the Piedmont section of North Carolina. He gave a history of alcohol and tobacco to excess. In his neighborhood there had been one death from pellagra, and there then existed two other cases. He had never had any serious sickness before the present trouble except measles three years before he came under my observation. From this sickness he dated his present trouble, as he said he had never been well since that time. Since this attack of measles he was constantly troubled with a gastric disturbance. On July 15, 1908, the present trouble began with nausea and vomiting and pains in his limbs, which he thought were rheumatic. Since this time, at intervals of about three weeks, he has had such attacks, which would last for ten days. In October, 1908, he was unable to walk or feed himself. In September of the same year he first noticed a stomatitis. During this first outbreak the only noticeable skin lesion was found over the knuckles and was of the dry variety. Although the winter of 1908 was spent in Florida under the most favorable conditions that money could buy, he continued to have these attacks of nausea, vomiting, and rheumatic joint pains at intervals of about three weeks. About June 1, 1909, the erythema appeared on the backs of the hands and also on the shoulders. The whole of the arms and forearms became affected with that peculiar lamellated erythematous condition which has been described on another page and which I count very distinctive of pellagra. The stomatitis had been present for nearly a year without intermission. Throughout the whole

[1] Osler, Wm., "Practice of Medicine." 1906.

year also the bowels had been deranged and the diarrhea did not seem to be aggravated by the coming of spring. Two weeks before the date of admission he became unable to walk. Vomiting was very persistent, and at this time I learned that two years previously he had vomited half a pint of bright red blood, though no definite history of gastric ulcer could be elicited. The patient was cachetic and had lost about forty pounds since the beginning of his sickness.

Examination showed the heart and lungs negative. Systolic blood pressure was 140 mm. of mercury, and the pulse was 120. The biceps and patellar reflexes were absent. The pupils were normal. At this time he was unable to walk without assistance. The gait was very unsteady and of a shuffling character, no effort to raise the feet in taking a step being made. Station was very imperfect, and he would certainly have fallen if not supported.

August 30, 1909. The degree of redness of the patient's mouth had greatly increased. He was having six bowel movements in the twenty-four hours. He could not stand alone without falling at once. By assistance he attempted to walk, but his gait was quite ataxic; his efforts to raise his foot high enough to prevent his heel from striking the floor was a failure. He was almost unable to cross his knees. All reflexes were abolished except those of the eye. Articulation was progressively more difficult until one was unable to understand much of what he said. There was a redness of his toes which was more suggestive of Raynaud's disease than the erythema of pellagra. The pulse varied from 120 to 130. Coördination was very defective and seemed to be more decided on the left side. He responded very slowly to questions and it was difficult for him to comprehend what you desired in the simplest questions. The urine at this time was negative.

September 2, 1909. Transfusion of blood was done by T. M. Green, the donor being a healed pellagrin, though a poor subject for such a purpose. The patient was stuporous and could not swallow without great danger of strangulation. He would slowly protrude tongue when told to do so. The stupor was gradually deepening. Occasionally he would take a deep breath, but between times his breathing was quite shallow. There was inconti-

nence of the bowel and bladder. There were indications of a return of the erythema of the hands. Pulse 140. Temperature 102°F.

September 3, 1909. Stupor was deepening into actual coma. He was unable to take any form of nourishment. Eyes were normal. At times there seemed to be present a slight nystagmus. There was slight twitching of the fingers. He died at 10 : 30 P. M. of respiratory failure.

A later inquiry into his nervous history revealed the occurrence a year prior to his admission into the hospital of an attack of some form of unconsciousness which lasted all night, and during the preceding summer (1908) he was unable to walk for some days, and his wife says that his gait and incoördination at that time were the same as now. It is very probable that this patient's nervous symptoms were functional without any underlying organic change. An autopsy could not be procured, much to my regret. It will be noted that this description differs from that of Osler's [1] two cases. In these cases there was no involvement of the sphincters of the bowel and bladder. It will also be noted in his cases that sensory symptoms occurred while none were noted in this case. Further, he rather emphasized the enlargement of the spleen, but, again, this change was absent in my case.

A condition which strongly suggests the possibility of ataxic paraplegia has occurred in my series of cases. As Marie believes that in many cases the distribution of the sclerosis is due to the arterial supply and not to a true systemic degeneration, it may be reasoned that such an occurrence would not be improbable in pellagra where there is supposed by Mariani to be a definite arterio-sclerosis caused by the disease. The increase of reflexes with ankle clonus, gradually developing rigidity of the legs not so marked as in uncomplicated cases of lateral sclerosis, marked incoördination and difficulty in walking in the dark or swaying when the eyes are closed, and to some extent the characteristic gait which is common to this disease is not an uncommon picture in certain cases of pellagra. One of the cases mentioned on a previous page well illustrates this condition.

[1] Osler, Wm., "Practice of Medicine." 1906.

The nervous symptoms occurring in pellagra during the early stages of the disease are usually of functional origin. The exceptions to this rule must indeed be quite uncommon and have no basis in the pathologic findings so far made in this country. My own experience is that many of the cases even of several years' duration are of functional origin. This opinion is based on actual pathologic findings, using the most approved technique of modern neuro-pathology.

Among the symptoms of this class more usually encountered are headache, chiefly occipital; pain in the back and in the neck; globus hysterica; sensations of prickling and formication; dizziness; general muscular weakness; uncertainty of motion due chiefly to weakness of the lower extremities. There also occurs psychical irritability, ill temper, complaint of giddiness and pressure in the head, disinclination to any form of exertion, and a high degree of mental weakness. It will be noted that the only distinguishing feature of these symptoms is the general indefiniteness and unlimited number. There is hardly a functional nervous symptom which does not occur at some time or other in some type of pellagra. In the second stage of the disease the following nervous manifestations occur: various parasthesias, especially itching of the backs of the hands out of proportion to the extent of the skin disturbance, itching of the back and occasionally of the lower extremities; burning in the shoulders, epigastrium, feet, hands, and arms, which is supposed to be the cause of the tendency of the patient, according to Lombroso, to leap into the water; formication; sensations of cold, chiefly in the lower extremities; globus hysterica; peculiar prickling sensations, more pronounced than in the first stage, occurring in various parts of the body; pain in the head, neck, and back, with a tendency to opisthotonus. The psychical symptoms which occur at this time will be mentioned later under a separate head. The motor disturbances are usually manifested by muscular weakness, chiefly of the lower extremities, which may be semi-flexed because of circumscribed paresis of the extensors. The observations of Procopiu and Tuczek are identical in regard to the motor disturbances. They both mention muscular

tension and tonic contractions of both upper and lower extremities. This may increase up to the point of tetanic rigidity. In many cases there also occurs a tremor of the arms, the head, and the tongue. Cramps, convulsive movements of single limbs, and, in some cases, pronounced epileptiform convulsions with loss of consciousness have also been observed. The patient mentioned on a previous page had a definite epileptic-like spasm some months before his death and his death occurred in such a seizure. It cannot be said that the occurrence of epileptiform seizures is a common event in pellagra. Out of four hundred cases collected by me I was able to find only this one case.

Disturbances of sensibility occur in pellagra at varying periods of the disease. In my experience the study of this condition has been very unsatisfactory, for the reason that the occurrence was late in the disease, when the mentality of the patient was such that replies to questions could not be relied on with any degree of certainty. Marie says that tactile and temperature senses remain intact, but such has not been my experience, as I have seen a marked perversion of both in many cases; but, as stated above, I am forced to modify my statements in this particular, owing to the inability of the patient to make intelligent replies. Marie again states that the sense of pain is diminished, especially in the legs, and that muscular sense is normal.

Tuczek stated that the gait in pellagra was paralytic usually, occasionally paralytic-spastic, but never ataxic, even in cases with an absence of tendon reflexes in the lower extremities; that static ataxia is occasionally mentioned; that incoördination of motion is mentioned only very occasionally and then only in the upper extremities; that symptoms suggestive of intention tremor have been observed; unilateral ptosis has occurred in a number of cases.

Marie with Roncoroni studied the electric reaction of the muscles and nerves in four cases. The patients had been for some time in the hospital of Turin and three of them were in good physical condition. The reaction of degeneration was not present and there was neither quantitative or qualitative deviation from the normal.

The electrical excitability was less in one than in the others and was attributed to malnutrition. He said that this was interesting for differential diagnostic purposes from polyneuritis, progressive muscular atrophy, amyotrophic lateral sclerosis, transverse myelitis, and other conditions.

Among the parasthesias was mentioned a sensation of burning which may occur in any portion of the body. It must not be confused with the violent neuritic pain which is so commonly complained of by the patient. This pain occurs chiefly in the palms of the hands and soles of the feet and is oftentimes a most distressing symptom. In my experience it has proven of grave prognostic portent. This pain is often so severe as not to be influenced by the full dose of morphine administered hypodermically.

Mrs. T. R., seen through the courtesy of W. F. Hargrove of Kinston, North Carolina, 27 years of age. She had no children and no history of miscarriage. Her general hygienic conditions were good. Family and previous medical histories were negative. Admitted on July 9, 1909. In June, 1907, she had an attack of symmetrical erythema on the backs of both hands and forearms, no stomatitis, but a slight diarrhea. In 1908 the outbreak was so slight as not to be well recalled. Late in March, 1909, erythematous lesions appeared simultaneously on both thumbs. In April the lesion involved the greater portion of the hand and a few weeks later blebs appeared. About this latter time a stomatitis appeared and the bowels became severely affected. There was considerable tenesmus with the diarrhea and sometimes the movements contained blood. About the middle of May neuralgic pains appeared in the feet, but there was no erythema in this part. This pain was chiefly in the ball of the foot and she described it as feeling as if some one was chopping it with an axe. The pain was so violent as to require an opiate. About June 1 the lesion appeared on the back of the neck unattended with bleb formation or pain. There was a slight lesion on the upper lids. There was no tremor, no clonus, and station was good. The reflexes were exaggerated to a very marked extent. Her mental state was good. The pain in the feet was never relieved and the same pain ap-

peared in the upper extremities. The doctor wrote me that up to the time of her death she continued to suffer violently, opiates having no appreciable effect. The case impressed me as being of the mild type and her death was a surprise. The only symptom that seemed to be of any importance after the diagnosis was made was this pain.

These neuralgic pains are a frequent occurrence in my practice, and I have often wondered why so little is said of it in the literature.

The vertigo of pellagra is a symptom which is referred to by all writers and counted of great diagnostic value. It often precedes the appearance of any other definite symptom. It is usually counted a neurotic symptom though some thought it was caused by a gastric anomaly of secretion. This symptom is not of so great value in the United States as in Italy. I usually elicit it but it has certainly no pathognomic value, and as it occurs in so many other conditions I do not think it is entitled to so much prominence. Often the patient complains of a "queer feeling in the head," and it is especially noticeable how rapidly this condition improves with arsenic medication.

The tremor of pellagra is often referred to in the literature and has been observed by the students of the disease in the South very often. It was noted by Strombio, the elder. Belmondo spoke of a tremor like that of the intention tremor in disseminated sclerosis, which is more marked in the upper extremities, especially in the fingers. Occasionally tremor of the head and tongue occurs. This tremor in my experience is more like a condition of clonic spasm than a real tremor. This clonic tremor is very coarse and unlike anything seen in any other condition. It is largely confined to the upper extremities, and I have never seen anything about it that suggested intention tremor. It seems to be much more often seen in women than in men.

The occurrence of contractures was mentioned on another page. Such a condition has not occurred in my experience. Marie says that in the movements and attitude of the pellagrous there is a tendency to certain contractures. When these patients rise it is

done with considerable difficulty. When the arm is extended it remains rigid and semi-flexed; sometimes the limbs are tightly drawn up. Often grotesque attitudes are assumed. Marie says that they squat down with the knees pressed against the chest and abdomen and cling to some object with hands or feet or even with the teeth. The result is often stigmata and characteristic deformities. I have often seen these poor wretches drawn up in bed with the head covered by the bed clothes as though in mortal terror of being seen. The whole body is intensely rigid and any effort to correct the strained position of the patient is followed by an immediate resumption of the former position.

There occurs in pellagra, though rarely, what Marie calls a partial chorea: that peculiar tendency to run in a straight line. It is said to occur more frequently in the morning hours. He says that there is also something which reminds one of epilepsy with ambulatory automatism. In typhoid pellagra the same writer observed contractures alternating with clonic spasms of the face and extremities suggesting electric chorea or tetanus and said to be aggravated by sensory impressions. It is often mentioned by the Italians that pellagrins have a tendency to fall backwards, forwards, or sometimes to the side as a result of the above-mentioned vertigo and sudden tetanic movements. Marie says this is what the people in pellagrous districts mean by pellagrous spells. Calderini reported this occurrence in 75 per cent of men and 77 per cent of women.

We read in Lavinder and Babcock's translation of Marie's work:

"General tonic spasms with trismus and subsultus appear under the influence of light tactile stimuli in many patients, just as in experimental animals. The opening or shutting of a door, the noise of an electric bell will sometimes provoke these spells. In one case tetanic rigidity persisted even during sleep, with elevation of temperature to 39 and 41° C. As long as they walk and eat patients have the sensation of a cord stretched across the back which draws them forward or to the side and they bend in that

direction. These attacks, because light and fleeting, might be called opisthotonic, emprosthotonic, and pleurosthotonic tetanus. 'The convulsions often have the appearance of tetanus,' says Allioni. Often contractures of flexion and extension result from them; some of them extend their arms in the form of a cross and remain rigid from four to six minutes; others remain whole weeks with the limbs extended and rigid, like katatonics; others have the sensation of a force which draws them by the head or obliges them to stiffen out the legs (Nardi)."

In the series of cases studied by A. Gregor the findings of Tonnini regarding the tendon reflexes were confirmed. These changes were: increase of the tendon reflexes, increase of the mechanical muscular excitability, tremor of the fingers, rigidities and spasms of the lower extremities, spastic gait, diminution of the tactile, thermal, farado-cutaneous sensibility, paresthesias, ataxia of the lower, in rare cases of the upper, extremities, and Romberg's sign. He emphasized the presence of muscular spasm and records the presence of tonic spasms in the terminal stage of the disease. He gives the following history illustrating this condition:

The patient lies stiff on his back, elbow and wrist joints flexed, as well as the knee joints, and the feet show plantar flexion. There is present in all extremities a severe form of spasm and a complete extension is impossible. He performs slowly extreme rotation and the arms are abducted and adducted in a jerking manner. When drinking motions are made in the presence of the patient he makes a jerky effort to raise his hands to his mouth, apparently resisting the involuntary contractions of the hands and arms, but finally he is successful in bringing the wrist joint of the spasmodically flexed hand near the mouth. The head is held in maximum spasmodic lateral rotation. On the next day jerking movements of the large muscle bundles of the lower portion of the face and of the forearm were observed. Gregor also observed clonic spasms in a female patient. To quote Allemann's translation of this article of Gregor:

"In the morning the patient lies on her back, the eyes are closed, the upper arms are adducted, the forearms flexed at an angle of 90°, which positions are kept fixed. In the region of the left lower facial nerve, I observed fine tremors which do not lead to any motor effects, also others, coarser ones, which draw the whole half of the mouth downward. The same tremors are also observed, though less severely, in the right lower facial nerve. The mouth is drawn a little to the left. Similar tremors of fine and coarse muscle fibers are also noticed in the sterno-cleido-mastoid and pectoralis on both sides. The upper arms perform adductions and abductions in a jerklike manner and the lower arms flexions and extensions. The thumbs are now and then adducted in spasms, the fingers flexed. Similar spasmodic movements are also observed in the lower extremities. There exist also spasms in smaller bundles of all muscles of the extremities.

"Passive movements find everywhere spastic resistance. The pupils react promptly to light and are of equal size, reflexes increased; spontaneous defecation and micturition. The patient does not respond when called by name, the face is distorted when pain is inflicted; the condition slowly disappears until the next day.

"In contrast with the first-mentioned case, no severe nervous disturbances were observed in this patient either before or after the appearance of the clonic spasms; on the other hand Tonnini observed clonic spasms only in the third stage of pellagra. Neither did typhoid pellagra exist in this case, a condition in which the patients are inclined to clonic convulsions (Lombroso).

"I would also mention that in some cases a paresis of the lower facial nerve was observed which in one case developed during her stay at the hospital. The occurrence of this disturbance is also remarkable as it is of value in the question of the relations of pellagra to progressive paralysis considering also the pupillary disturbance in the third stage. While Baillarger once tried to prove, in opposition to Verga, that pellagra may be followed not only by mania and melancholia, but also by progressive paralysis, the question is rather analogous to that of specific alcoholic paral-

ysis: Is there a form of paralysis produced solely by pellagra? The question is answered affirmatively by Pianetta, negatively by Verga.

"Among the anomalies of sensibility, the disturbances of faradocutaneous sensibility are strikingly marked, on account of which I tried to determine it exactly on the skin of the forearm, which according to Tonnini is especially non-sensitive to faradic irritation. In all cases examined, I found extreme weakening of sensibility."

I have noted the clonic spasms recorded by Gregor, but, contrary to his expressed view, I count them a part of typhoid pellagra which he says was absent in his case. Certainly this symptom has never occurred in any case except a short time before the termination in death. I have never seen it in the acute or fulminating cases even though they proved fatal. It is a very characteristic manifestation which once seen is never forgotten nor confused with any other condition. It is so characteristic that more attention should be paid to it, and its value both from a diagnostic standpoint as well as from the viewpoint of prognosis should be more emphasized.

It will be seen then that the manifestations of pellagra on the spinal cord are even more diversified than the cord manifestations of syphilis, and it is impossible to describe any one condition of the cord which is distinctive of it. This is a fact of great importance especially in pellagrous sections or in patients from such localities. The neurologist must add this possibility to his list in taking histories of patients with spinal cord symptoms.

It will be seen that the changes in the cerebrum in pellagra are not so definite even as the changes recorded in the cord, though it must be acknowledged that too little neuro-pathologic work on the cerebral cortex according to the most improved modern methods has yet been done, especially in the United States. At this time we can only say that in many cases manifesting marked psychical disturbances the pathologic changes were absent or insufficient to account for them.

The time of the appearance of mental symptoms in pellagra is subject to all possible variations. The reader will recall the case of the grocer who was supposed to be suffering with a symmetrical gangrene of the skin due to malaria and which was later found to be pellagra. In this case the mental disturbances antedated all other symptoms by many weeks. On the other hand I recall the case of an old man who told me that he had been pellagrous for forty years and yet he was able to make his living as a laborer and manifested absolutely no symptoms of the disease from the mental standpoint. This brings up the very interesting question as to whether the numerous cases of pellagra in the insane in southern institutions were of pellagrous origin or were instances of the engrafting of pellagra on a preëxisting mental disorder. It also calls for an answer to the query as to whether or not the insane are peculiarly susceptible to pellagra. I have in mind the case of a woman who was an inmate of an insane institution for four or more years before the first symptom of erythema appeared. Her brother later developed the same type of insanity but the full picture of pellagra never developed; his distinctive symptoms being merely stomatitis and diarrhea, which may occur in other forms of mental disorder. It is likely that many cases of pellagra have been overlooked on account of the mildness and very limited character of the erythema, and again, it is not improbable that many of the cases observed in some of the American insane institutions presenting erythematous lesions of the hands and diagnosed dementia paralytica were truly pellagrous. We recall the opinion of Siler that pellagra occurs in practically all the insane institutions in the United States.

There is nothing distinctive of the mental symptoms of pellagra and the picture varies almost as much as did the cord symptoms. The only one characteristic which I have uniformly noted is the depressive type of psychosis. This observation is borne out by all observers. Delusions of grandeur never prevail, but delusions of persecution are exceedingly common. It is said by most writers that these patients are never dangerous, and as a rule this has been my experience though an exception will be later noted. Grief

over imaginary sins and short-comings has predominated the psychic picture of so many of my cases that I have often been tempted to count it of considerable diagnostic value.

In the earlier cases which occurred in the United States, as would be expected, psychical symptoms did not play any great part and many patients died without manifesting the slightest evidence unless a general depression is placed in this category.

Gregor's first classification is called neurasthenia. My cases have manifested symptoms of this condition as a part of a development of a more serious state. He says that in this group he places patients who manifest symptoms of headache, pain in the gastric region, pressure in the head, vertigo, lassitude, depression, a sense of unrest which is stressed by Tuczek, anxiety which may be increased to phobia, fear of something undetermined which is threatening, a sense of bodily and mental incapacity, and of illness. The patient appears well behaved, not disturbed intellectually but incapable of mental or bodily activity of any sort. He claims that the process of association is decidedly disturbed and the simplest questions are often answered only after long hesitation. I have been deeply impressed with this peculiarity of these people. Sometimes this retardation is so great that the one asking the question will almost forget it before the reply comes in a drawling, stolid fashion, reminding one of a very deaf person who, not hearing but a portion of the conversation, continues on the subject heard long after the general conversation has moved on. The tone in which these replies come reminds one of that peculiar type of utterance heard so often in opium habitués. The spirits are depressed and the patient appears anxious. Hypochondriacal notions are often recorded which Gregor says receive new stimulation from the subjective troubles from the consciousness of being pellagrous and from their own experience of former serious sickness. There is sometimes motor unrest and a constant tendency to be on the move, but the physical condition often has a greater tendency to produce motor impediment and the patient becomes markedly apathetic, not being willing even to get up for a movement of the bowels. Stolid indifference is also a characteristic of these pa-

tients. This indifference manifests itself in several ways. A mother will become utterly indifferent to her child even though it be an only one. A man who had been hitherto most careful of his dress becomes most untidy, not from a change in disposition *per se* but because of this lethargy.

There seems to be a kind of sensitiveness on the part of the victims of pellagra and they will conceal the fact of their affliction to the very utmost, as though it were a disgrace of which they were ashamed. This peculiarity is really a neurasthenic manifestation according to my observation. It seems to be more pronounced among the Italians than in this country.

Of the 72 cases studied by Gregor 7 belonged to this neurasthenic group.

Gregor's next subdivision is acute or stuporous dementia. Of his series 10 were thus classified. This group includes mild cases which are merely exaggerations of the neurasthenic class. All the symptoms above referred to are accentuated and the psychomotor disturbance is increased to stupor. Such patients lie for weeks in an apathetic state and in order to impress them with a question it is necessary to repeat it with marked intonation, as Gregor says, and the reply is made with great effort in the simplest terms or no answer at all is heard. I have often noticed that in those cases where no answer is given there is an expression of intelligent appreciation of what is desired of them but a motor inability prevents the reply. Requests to do anything are followed out with hesitation and effort and the resulting action may be stopped in its first phase, or the request may be forgotten before the execution is completed. This is very characteristic and was well illustrated in the case detailed on page 243. Gregor says that these patients are fairly well oriented and that the psychic activity is often revived for a short time. In the height of the disease orientation is sometimes definitely disturbed. Illusions of varying nature were present in all of my cases reaching this stage of pellagra but there was an absence of any distinctive quality. There is usually noted that lack of confidence in oneself which is almost a timidity and which is so often noted in psychasthenia. It is

a notable fact that these people possess a consciousness of their psychic deficiency as well as a general hypochondriacal point of view. This is as true in my own experience as it was in Gregor's.

The following letter was received from a patient who was on the border line between this acute dementia of Gregor and his neurasthenic group. The patient called at my office but had nothing to say. On leaving, however, she handed me the following letter, which was written clearly and connectedly.

"Dear Doctor, — I guess you will think I am foolish but I am going to tell you my story, of all my sufferings of this past summer. I shall tell you nothing but the truth, so help me Heaven. Now, I was always of a happy disposition, always looking on the bright side of everything, always had a laugh and a joke for all; not what you find me to-day, a wreck of my former self. Well, to my story, of how I have watched the development of this disease, calmly, for I knew I was coming to you for treatment if not cure. Last April I had a terrible fever, bad trouble with my bowels, and nothing could be done that would cure me of all this trouble. I was sick this way for several weeks and could eat nothing; my mouth, throat, and stomach seemed to be on fire. Along in April the eruption appeared on wrists, hands, and throat. Well, I seemed to get better of the dysentery and was feeling pretty well, but the eruption spread rapidly, soon getting to the elbows. . . . The eruption appeared again and soon spread more rapidly than ever; a new spot appearing above each elbow and on each shoulder, I did not treat it right off and it soon covered my arms, neck, and shoulders, burning fearfully.

"In August Dr. X. began treating me and to look back and try to remember the treatment I welcome the disease. Pellagra causes insanity and awful suffering but is slow in its progress, but I found this treatment awful in its rapidity in causing insanity, as you will see by the following, my recital of his treatment. When I started his treatment I thought I was a sick woman, but when I left him I was one hundred times worse than when I began. Of course my memory has been failing me a long time and I was

somewhat giddy when I began with the doctor. Well, the first week he gave me a lot of things to take, among which was something that was to be taken three times daily and increased just one drop a day until he told me to stop. The first week, also the second, I thought I was better. The first hypodermic was in my arm. I felt no effect of it, but the next was in my hips. The second injection made me feel like a new woman. I had not a care in the world, or it seemed that way. The next time I went the injection made me so sore and stiff until I could hardly walk. I could not lie on that side for several days. The next time I went to him I asked him if it was the same kind of injection, he said it was, I told him how it affected me, he said it belonged to act that way, so I kept going to him every two nights, getting worse each day. Oh, I shudder now, as I try to think and my mind gets more confused as I try to tell you how I suffered. God in his pity for my ignorance saved my reason. I would have gone insane, anyway, if I had not asked God to help me until I could come to you. Before going to the doctor I had good nerve and good will power, so I did not worry for I knew I was coming to you, and I would bear all patiently. I lost most of my weight after this treatment. Any of my friends will tell you that. Well, after a while I began to get more giddy than ever; I seemed to be stepping down, down, down; muscles seemed to contract, lost nearly all power of my fingers and wrists and arms. Every joint I had seemed to be getting paralyzed; I had to grasp anything I could find to keep from falling, so giddy was I. My whole brain seemed to grow more blank after each treatment. My head had a roaring sensation, and in about four weeks time, I had forgotten home and friends, even my God was forgotten.

"I could not eat, he said he did not wish me to eat much. The dysentery began on me and each time I went to him I told him he was killing me; he said I would be soon well. . . . I knew I was an idiot for taking another treatment of him but my brain was awfully weakened, and I kept going, getting worse each time. One night my left ear seemed to burst, such a roaring, stewing sensation in it. My eyes were almost ruined. I could not recog-

nize my husband fifty yards away. I could not read a line, the letters seemed to all mix and dance before my eyes and I grew so sick and nervous as I vainly tried to read; I would be quivering all over and my head would seem to be rocking back and forth. I seemed to be falling on my face when I walked. My arms would seem to try to come to my chest and fold there. I had to keep them straight. My knees were in the same awful fix. It seemed like I was going to fold up, every muscle contracted, and I felt like I was being drawn to the earth to rise no more; two large sores came on my neck and one under my left jaw; also one above my left brow and one on the edge of my forehead, all on the left side of my face. He said it belonged to be that way, and gave me sodium phosphate salts, effervescent. Oh, that ruined my mouth and stomach. Made the hemorrhage worse, gave me awful dysentery. I thought I must die the last three weeks he treated me. I could hardly dress myself to go to the doctor.

"My husband had to bring the buggy to the door and lift me in many times. My right ear had the sound of guns firing in it, low muffled sounds; that horrible itching, burning in my head was ever present, getting worse each day. I could only stand twenty-four drops of that poison he gave me to take, I took it until I had taken eight drops three times on the last day, told him I could not take more at that time. The hemorrhage (menorrhagia) was so bad I must die. Oh, I was in the most awful condition. My mind grows dark as I think, but the more I went to the doctor the worse I grew, my mind seemed to be gone, my brain was in the grasp of some awful something. . . . Well, I was so numb and paralyzed and foolish and kept getting worse all the time. I seemed to forget everything, my saviour as all else in this blind, awful suffering. . . . I hope you can save my reason, I feel like an idiot but hope you, with the help of the most High, will make me like I was before taking this medicine, yes, even that clear-minded. . . . I have fought this madness each minute, saying I would not go insane. . . . My brain would grow so dark that I forgot god and family, forgot everything save this awful despair. I would have awful times of weeping, and that saved my reason, I think, as my mind

would clear for a few days, but settled back to the same old way. I have had two spells of weeping since being here, but I know I am better."

The fixed idea of this patient that she had not received the proper medication was, of course, absurd. I think she would gladly have died if she could have had the satisfaction of knowing that the physician had caused it. She was most insistent in her entreaties that I would acknowledge that he had done her harm. As she improved this peculiar mental phase somewhat subsided, and now she never refers to it at all, though it is not probable that she has entirely recovered from her unreasonable prejudice.

This same patient later wrote from her home the following:

"And I must tell you the shameful truth, that I only crave such things as earth and ashes, charcoal, and such things that a human should not eat. I never gratify my depraved appetite. Have had this abnormal craving for the past year. Now, please do not laugh at all this for it is true and I cannot help it, but I thought you should know. I think the worst symptom I have is that dreadful, creepy, itchy burning sensation in my ears and scalp. I can tolerate all the burning and the other bad feelings I have, but this last I 've mentioned makes my brain feel so queer and confused and idiotic. . . . I dislike to air my troubles to any one and do so as little as I possibly can."

The home of this patient is in the very heart of the hookworm section and I am inclined to think that her statement of a vicarious appetite is purely suggestive, brought about by the lectures and demonstrations of the Rockefeller Commission for the Eradication of Hookworm Disease. It is not at all improbable that she might have really had the sensation complained of, though in many conversations she never made any reference to it. Certainly she was a typical victim of the hookworm infection. Hypochondriasis was very marked and she would never tire of telling of her peculiar sensations. She never developed the lethargy and indifference so

often noted but, on the other hand, she was always very active mentally as well as very sensitive. Fear and dread of insanity was her constant plaint. A letter of only a few days ago announces a fresh outbreak and I am surprised that she seems to be taking it very philosophically and does not refer to insanity. Her mental condition has greatly improved during the winter as has her physical condition, and my last note records a gain of twenty-three pounds since last November when I first saw her.

In many cases there is a very gradual development of the stuporous condition. In these cases Gregor states that there is a disturbance of psycho-motor activity without vivid mental disturbances. It is further stated that some patients recognizing their mental unfitness apply for admission to the insane institutions. I have never experienced this, but it is no uncommon thing for them to acknowledge their insanity though the expression is usually of a fear of its subsequent development. There is often seen a gradual development of an " affectless stupor " which is followed by a return to their former mental condition. In some cases psychic impediments are said by this same author to develop in a relatively short time. The feeling of mental insufficiency, as in the above-mentioned case, is apt to have a very melancholy aspect and in some instances there may be manifested suicidal tendencies. It is also noted by Gregor that severe cases may assume temporarily katatonic symptoms of posture and motion stereotypies.

Tanzi noted disturbances of memory in this group but Gregor says weakness of memory is not a characteristic of acute pellagrous dementia and that in convalescence memory readily returns, determining that the supposed disturbance of memory was really due to difficulty in performing psychic processes.

Melancholia is the usual mental disturbance in pellagra, and it is said that with the improvement in the physical condition there will be a corresponding improvement in the mental state. Such has usually been my experience with a few exceptions. One of these exceptions is the case of a woman who has not suffered an outbreak for so long a time that she is counted well of the pellagra but she insists that she has only a few more days to live and has

regularly sent for one of her children once a week for many months in order that he should be present at her death. Tanzi considers these cases of melancholia to be really a mild form of amentia. Gregor counted stupor to be an unfavorable prognostic sign.

Of this group of acute (stuporous) dementia Gregor had ten cases of his series of seventy-two.

Gregor's third group, of which he had thirty-two cases, is the amentia or acute confusional insanity. He says that they were long continued with a tendency to remissions and intermissions. There is first a period of varying length manifesting symptoms of a neurasthenic character, followed by terrifying hallucinations to which is added violent motor excitement. According to Gregor delirium was followed by stupor or the stupor was interrupted by delirium. He says the patient sees the house or village burning, enemies coming, wild animals attacking him, and the devil appearing; that more rarely there is a quiet, dreamy state and the heavens open and the Lord appears and in imagination they return to the scenes of their daily life. There occurs phenomenon of motion in connection with hallucinations. When secluded they are prone to move about and become noisy. The period of excitement lasts from a few hours to several days. These outbreaks may be followed by long intervals of mental and bodily quiet. Stupor may occur but there is only slight disturbance of orientation. Later in the course of the disease they are said to pass into a delirium of the same character as seen in typhoid fever or meningitis. In the presence of diarrhea added to this mental state, Gregor finds his conception of typhoid pellagra. Hallucinosis is said to offer a decidedly favorable prognosis for the first attack. Further it is stated that dementia does not always ensue after a severe initial attack. The development of katatonic symptoms, which is more apt to occur in juvenile cases, makes the diagnosis more difficult.

Gregor's fourth classification was that of acute delirium, and of this group he reported two cases out of his series of seventy-two. This class is distinguished from the third or preceding group by an exaggeration of all the symptoms of that group. There occurs

a condition characterized by hallucinations, motor excitation, and a shorter course than the preceding which ends in death. These symptoms are said to occur in some instances without the bodily signs of pellagra though the two usually occur together. Except for an absence of a rise of temperature the second, third, and fourth groups of Gregor's classification are said to resemble the mental symptoms of acute infectious diseases and for that reason are arbitrarily placed in a classification under the infective exhaustive psychoses.

Gregor's fifth group, designated katatonia, is so different from my own experience that I quote the whole:[1]

"The katatonic condition occurs with acute somatic pellagra. Here, considering the concurrence of acute somatic and psychic pellagra, we must assume a pellagrous intoxication as to the causative factors, as in pellagrous neurasthenia. Many patients show consciousness of their disease. Hallucinations may precede this condition. Excitement, stereotypy, wild jactitation and verbigeration are common. The katatonia cases pass rapidly into dementia.

"Of the cases of the fifth group, the majority belong to the katatonia subdivision from the symptoms, course, and termination. In all three cases (females) excitation occurred, ending with stereotypy, jacitation, and verbigeration. The patients did not show marked effects. In one case, hallucinations preceded the condition. In all three cases, the transition into dementia was rapid, in which posture and motion stereotypies, impulsive actions, and talkativeness were observed. In one case, these symptoms were followed by a permanent negative phase. In another case, besides many posture and motion stereotypies, interchange of negativism and flexibilita cerea was observed. In one case, the katatonic symptoms were marked from the beginning. A male case showed on admission to the hospital katatonic excitation, and after a few days a remission followed by another katatonic phase.

"Six of these cases ended in dementia more or less rapidly, although remissions may occur."

[1] "Pellagra and the Psychoses," by J. W. Babcock. *Am. Jour. Insan.*, 1911.

The sixth group of Gregor is the anxiety psychoses. Of this group he had three cases. He says that the violent, fluctuating anxiety effect, the motor unrest, the anxiety ideas, and the "phonemes" completing them, determined the diagnosis. It is complicated, however, by extraneous features. There is shown a sense of insufficiency, and the victim appears stuporous in the intervals between attacks resembling cases classified under the second and third groups. Mental weakness increases after the anxiety attacks have disappeared. Psycho-motor weakness alternates with violent anxiety effects and vivid motor unrest. Temporary ideas of persecution and sin followed by stupor were observed by Gregor. One case of this group was typical depressive melancholia.

The seventh and last group of Gregor was manic-depressive insanity and two of his cases were thus classified. One showed the condition of mania arising from subjective pellagrous troubles while in the other the mania was followed by a distinct stupor.

The classification of Mobley is as follows:

(1) Acute intoxication psychosis, with psycho-motor suspension.

(2) Infective-exhaustive psychosis, with psycho-retardation or excitation.

(3) Symptomatic melancholia, with psycho-motor retardation.

(4) Manic-depressive, with psycho-motor retardation or excitation.

The following correspondence from a man whom I had known in college is interesting. He was a school teacher and well educated. Many of the letters received from pellagrins would show even better the mental states but for the fact that the majority are not well enough educated to express themselves in anything like a normal manner, and again at the time of marked mental change there usually occurs sufficient motor disturbance to interfere with writing. The character of the handwriting itself shows early tiring. The letter reproduced on a previous page of this chapter was written by an educated woman also. In the beginning there was no error but it will be noted that very soon mental exhaustion manifested itself in carelessness in punctuation and in failure to use the capital letter in speaking of the Deity.

"I have a dark feeling day and a bright one succeeding each other. I feel on my better days that I shall soon be well. I have many optimistic thoughts. On my darker days, my thoughts are pessimistic and it seems to me that my case cannot be cured. This better and worse day has been true generally but not always as sometimes I have had two bright days together.

"All of that tickling and prodding feeling up and down my spine has now ceased, and I no longer feel so much head swimming. My thoughts wander or move slowly and are not capable of concentration to any great extent. I am improving in this matter. This is the part especially that I want to improve right soon as I think I will when the medicine has acted freely. . . . Truly, I did not take the case so seriously until the last day or two. I see that it is certain that I shall give up my school work and move back on my farm by January next. . . . I would like to have space to write you fully of the terrible head swimming and dreadful gloomy feelings that I have experienced. Mainly all these feelings have passed off now. Somehow as before stated I cannot fully apply my thoughts yet. You may know I am thinking of the awful death ahead of me and the motherless children that I shall have to leave. Of course I want to think that I will live a few years."

Following this letter in a few days the following was received from the same patient.

"Dear Sir, — I wrote you some time ago as to my sickness. Now it seems that my blessed reason is returning and I write you more of my illness.

"Doctor, please tell me whether committing sin or moral wrong will bring on pellagra. Somehow my affliction appears to be of Divine infliction. I want to get well. I am willing to confess any wrong if necessary. As only a very slight sample of my ungodliness is embraced in the letter to Miss X., I am sure you will understand my letter to her well enough to apply it in any and all ways for the best. I feel somewhat that I may

recover. God's people are praying for me. The above is my own writing. Thank the Lord for this improvement.

"Your obedient servant."

This man's idea of having done some great wrong proved to be, on careful investigation, a pure delusion. The letter which was enclosed would impress one as being merely an expression of an over-conscientious individual making of a mole hill a mountain. Over-conscientiousness and fear of imaginary wrongs or imaginary deficiencies occurred in so many of my cases as to impress me as being characteristic. One man who had been an engineer for a railroad company for over twenty years was obsessed with the idea that he had defrauded his company and that all of his surveys were erroneous. Finally after great mental anguish he went to his employers and confessed to faults and errors which he could not be persuaded were not true. It was a well-known fact that all his life he was conscientious to the last degree and one of the most trusted in the company's employ. He soon shifted his anxiety to the fear that his religious expressions were not sincere and that he was sailing under false colors in holding a prominent position in his church. Soon after I was sent for because he said that the health department had sent a police officer to arrest him because his house needed fumigation. He insisted that his bed and his person were covered with bugs and in order to quiet him it was necessary to pretend that a fumigation was being done. This insane idea was only temporarily relieved and reappeared in a few days.

Another patient, referred to in a previous chapter, told us in great distress that she was not lawfully married to her husband and that her children were illegitimate. This was the first evidence of an active insanity and we were not at all suspicious of the delusional character of the statement until later in the course of her disease it was shown that there was not a vestige of truth in it.

Over-conscientiousness, as before mentioned, a feeling of insufficiency and lack of confidence, and various religious ideas,

especially a fear of the unpardonable sin, delusions of persecution and fear, profound melancholia, together with indifference were the most common symptoms of mental change in my cases. It is impossible for me to fit my cases into the classifications of Gregor in every instance, though his classification comes nearer to filling the requirements than any other. It will be noted that the case of the school teacher who wrote the letter above fits well into Gregor's sixth place, that of the anxiety psychoses. To the question: Are there disease pictures of dementia, whose anatomical basis is an injury to the brain by the toxins of pellagra? with Gregor I would unhesitatingly reply in the affirmative.

Acute delirium, which is Gregor's fourth group, occurs frequently in the American cases. Repeatedly it was necessary to restrain these patients. Mutism and various flexures of the extremities are noted in such cases. They lie doubled up in bed attempting to conceal themselves beneath the bed clothes. The peculiar clonic contractions of the upper extremities are also noticed. The outcome in such cases is invariably fatal and the condition is the expression of a terminal state.

Salerio epitomized the mental conditions of his cases thus: a frightened state, ideas of persecution or belief that they are possessed with the devil; a suspicious state, the refusal of food and medicine; and an exalted religious state. Suicidal tendencies were noted by him. He said that finally they are liable to lapse into dementia, paralysis, or tubercular disease.

Lombroso found that one of the characteristics of the pellagrous psychosis was a greater moral impressionability; that a slight insult or the threatening of some trivial danger completely possesses them. He thought that if pellagrous insanity assumes a type it approaches that of chronic mania and dementia more closely than monomania. The real or apparent stupidity and the obstinate mutism Lombroso called "psychical catalepsy." But Babcock, commenting on this expression of Lombroso, says that the insanity is of "a misty, ill-defined contradictory character, like that produced by old age, or by anemia, and differing in this point from general paralysis."

Babes and Sion found the psychical symptoms appearing several years after the first appearance of the disease. The first symptom noticed was mental weakness. The pellagrous insanity was preceded first by spasmodic then tonic cramps and general weakness with a final development in a true pellagrous paralysis. They state that the cramps of the feet, hands, and calf muscles are sometimes so violent as to result in epilepsy, contractions, and swooning. They also state that so-called pellagrous epilepsy is the result of pain. This is certainly not always the cause, as is illustrated in the case of pellagra occurring in a patient suffering with tertian and quartan malaria, which was recorded on another page. This patient died in a convulsive seizure and had never complained of pain at any time during the two years he was under observation, nor was there manifested any evidence of pain at the time of his death. They mention the so-called pellagrous tetanus (Strombio) in which opisthotonus was a symptom. It is stated that sometimes the patients are drawn forwards and fall to the ground. Choreiform movements were noted and were more frequent in the head. Roussel mentioned the important fact that delirium does not occur until the spring of the second or third year. It is further stated that sadness may advance to mutism and refusal of food, but there may be an interruption in the form of attacks of weeping or of suicidal or maniacal outbursts. An acute attack leaves the patient in a state of exhaustion, depression, and hypochondria. With each attack the intellect weakens and dementia gradually develops.

Babes and Sion conclude thus:

"Pellagrous melancholia shows various stages: at first, there are psychic impediments, followed by apathy or stupor. Delusions of sin, of persecution appear. Mania is rare but catalepsy sometimes occurs.

"When paralysis supervenes, euphoria appears, presenting a disease-complex like general paralysis, but even in advanced stages of the diseases remissions may occur."

Antonini gave as his opinion regarding this complex problem of the pellagrous psychoses the following:

"Already in the first stages of pellagra there appears a decided modification in the mental faculties; there is a great impressionability, a greater psychical excitability, a slight disappointment depresses greatly the tone of feelings, or produces excessive reactions (from the want of initial inhibitory powers). In the progress of the disease we can have true amentia, states of mental confusion common to all psychoses arising from exhaustion. This state can show suddenly an exaggeration of symptoms and lead to death with a syndrome of acute delirium (typhoid pellagra) and yet it can also present in certain cases a true progressive paralysis of pellagra.

"But a frequent symptom is the obstinate refusal of food, such as aggravates painfully the already sad picture of the pellagrin."

I have noticed that in some of these cases where there was this obstinate refusal to take food in any form, that if it was left in reach of the patient and the patient was left alone that the food would be eaten.

In a few words Allbutt well states the condition under discussion. He says:

"When the patient has thus been the subject of the disease in its recurring attacks for three or four years his depression of spirits deepens into melancholia of a severe and irremediable kind. He commonly suffers from globus. The melancholia may be altogether dull and heavy, or on the other hand it may have maniacal phases: the patient may be moody, self-accusing, and remorseful, or he may present maniacal periods, in which misery or a horrible burning of the skin may drive him to suicide. Systematic monomania ('paranoia') is never seen. As depression may alternate with mania, so stupor may alternate with the vertigo; and twitchings, tremors, and even epileptiform seizures of the cortical variety are not uncommon."

In many cases of pellagra are seen symptoms that would justify the classification of amentia. The clouded consciousness, interference with association memory, hallucinations and delusions, anomalous emotional states as apprehensiveness and fear are often present in pellagra and are also distinctive of amentia. Paton,[1] who well describes this condition, says that there is no sharp line to be drawn between this condition and acute delirium; many cases can be differentiated only by the longer course in the former. In the description of amentia is found reference to a condition in which the patient shows signs of restlessness, slight dissociation in connected thought, apprehensiveness, and fear of being left alone. It is recorded also that he will complain of unpleasant thoughts and unpleasant dreams. Disturbance in association memory increases and distractibility keeps the attention constantly wandering, so that when asked a simple question the patient begins to reply, forgets the subject in hand and passes to something else. All of these symptoms may be noted in pellagra. In both conditions hallucinations hold a prominent place. Ideas of persecution are noted and the patient suspects the physician and attendants in both states. It is said that in amentia the character of the hallucinations in the early stages is constantly changing. Motor restlessness often associated with extreme talkativeness have been noted in both. Paton says there are two types of this disease: "an asthenic type and one in which the confusional state is more boisterous and the general motor restlessness greater. To the former belongs this confusional or stuporous amentia of Meynert; to the latter, the hallucinatory confusion, delirious amentia, and the so-called acute hallucinatory paranoia of other writers." I am of the opinion that many of the psychoses of pellagra are true cases of Meynert's stuporous amentia and that the etiological factor is the pellagra poison, whatever that may be, just as parturition is a recognized cause of the same condition.

[1] Meynert, "Die acut. hallucin. Formen des Wahnsinns u. ihre Verlauf." *Allgemein. Ztschr. f. Psych.*, XXXVIII. *Jahrbuch. f. Psych.*, 1881. Chaslin, "La confusion mentale primitive," 1895. Del. Greco, "Sulle varie forme die confusione mentale." *Il Manicomio moderno*, 1897 and 1898. See also for these references and his views quoted: "Psychiatry," by Stewart Paton. 1905.

It must be remembered that certain catatonic symptoms occur both in amentia as well as in dementia precox, and these catatonic symptoms are not unusual in pellagra. In dementia precox, however, these symptoms are much more definite than in the other conditions, while in amentia there is greater impairment of consciousness and more defects in association memory.

Many cases of pellagra suggest the diagnosis of manic depressive insanity, and this condition, too, is easily confused with amentia. Paton says that in genuine cases of mania the flight of ideas has certain specific qualities and the interference with consciousness or with the reception of all forms of sensory impressions is less marked. The very fact that in this group of manic depressive insanity there occur phases of melancholia which later are replaced by mania suggest just the condition in pellagra, but it must be said that the same alternation of phases also occurs in other mental states. During the motor phase of manic depressive insanity the general restlessness, the psycho-motor activity, the lack of coördination of movement with the peculiar jerky and impulsive actions, sometimes also tremulousness and unsteadiness would not be foreign to the psychosis of pellagra. But the animation, the obtrusiveness, the tendency to be meddlesome, and the grandiloquence would be very foreign to pellagra. In pellagra I have seen maniacal states but they were never of the violent type seen in manic depressive insanity. During the stage of depression in manic depressive insanity occur symptoms which are very suggestive of the pellagrous psychosis. The tardiness in replying to questions, the emotional depression, the change in handwriting due to retardation of voluntary movements, " the consciousness of subjective difficulties in the association processes," vague apprehension which is often increased to marked anxiety point strongly to pellagra.

The psychosis of pellagra does not materially differ from the other psychoses in the sense that the whole symptom complex must be considered making due allowance for the various phases which are constantly changing in so many different states, in arriving at a diagnosis.

A case of pellagra during the inter-eruptive period removed from a pellagrous locality might tax the resources of the psychiatrist for a while, but the probability is that the record would show the diagnosis of amentia of Meynert in the majority of instances.

The following record is from my case book under date of August 6, 1909. The changing phases of her mental state make it an interesting case. The difficulties of classification will at once be apparent.

Mrs. L. H., Bladen County, N. C. Age 41 years. Mother of five children; the youngest child is fifteen months, the oldest fourteen years. No history of miscarriage. She is fairly well conditioned.

Family history has no bearing on present condition.

She had never been sick until the present trouble began. In the spring of 1903, six years ago, she had a painless diarrhea and a stomatitis. This recurred every year for six years. In the fifth spring she noticed the first signs of an erythema. This year the trouble began on May 1 with the following symptoms: stomatitis, diarrhea, marked salivation, globus hysterica, and a very disagreeable salty taste. Sometime after this the characteristic lesion appeared on the backs of the hands with some desquamation which the patient said had existed from the beginning. Physical examination of chest and abdomen was negative. She complains of "stinging all over" and at the same time says that her flesh is dead and numb and the feet and legs burn like fire. Her memory is bad and she is very despondent. She sleeps very badly and has had only one night's sleep without drugs in a month. Her appearance is that of a woman twenty years older than she really is and I was amazed when I was told her age. She has signs of marked cachexia. Her expression is anxious. Pupils react almost imperceptibly to light and imperfectly to accommodation. Station is unimpaired. The patellar reflex is diminished. Pulse is weak and the rate is 128. Systolic blood pressure is 105. The patient says: "When my flesh died I lost control of myself and I now breathe through powders and my nostrils are too open and I

breathe too freely." She appreciates her mental deterioration. At present her mental state is characterized more by hallucinations than delusions. Hemoglobin, 85 per cent. Red cells, 4,500,000. Whites, 9,400.

August 15, 1909. The knee jerks are found quite variable, differing frequently from the biceps jerks which too are subject to marked variations at different times. The patient insists so persistently that worms are present in her vagina that an investigation has had to be made to satisfy her, but she acknowledges that she has never seen any of the worms. Of course, none were found. She volunteers the opinion that she is crazy.

August 25, 1909. The language of the patient has become very obscene. She is exceedingly restless and cannot be kept in the house. Her people are becoming afraid of her. There is still a melancholy cast to every mental phase. She has definite delusions of persecution and talks of protecting herself. When I remonstrated with her about talking so improperly before the children and about her calling them improper names I could make no impression on her or even hold her attention.

A few days after this she was found with an axe roaming aimlessly about the yard in search for some imaginary person on whom she wished to use it. It was not thought prudent to leave her at large so she was committed to the State Hospital for the Insane where she died in a few weeks.

The following case is much more characteristic of the mental condition of pellagra.

M. C. Female. White. Unmarried. Age 43. Farming class well conditioned. Seen September 29, 1910.

Family history has no bearing on present condition. She was never sick until the spring of 1903, when she says she began to decline and in November had typhoid fever. At this time vague nervous and mental symptoms of long standing were exaggerated. After the fever she regained her full strength and remained well until the present year. In May of this year her bowels became

affected. This was accompanied by stomatitis without salivation. During June it was noticed that her mental state was not normal. Her mental symptoms were characterized by over-conscientiousness and self-condemnation. She thought that all the trouble in the world had been caused by her. She had the fear that someone was taking her home away, and besides this particular fear she was afraid of everyone and desired to be left alone. She attempted suicide by jumping into the well. Her complaint was of pain in the top of her head. The intestinal disturbance lasted several weeks. She was dizzy but never had fallen and she complained of weakness. She said that she wanted to be helped to do right when I questioned her regarding her reason for consulting me. There was a history of insomnia of a very obstinate type. She imagines the presence of people and hears peculiar sounds. She thinks that she is insane and volunteers the information that her condition now is the same as after the attack of typhoid. Replies to questions are inaccurate and given with great tardiness. She is careful about her clothing and appearance.

This patient recovered and has been in good health for over a year. All of the mental trouble has disappeared and to all appearances she is normal.

The following conclusion of the whole matter by J. W. Babcock is worth quoting in full:

"The association of pellagra with nervous and mental symptoms is common. This relationship is that of direct cause and effect, and is not an accident or coincidence.

"Cases of pellagrous insanity have usually suffered from pellagra with neurasthenic symptoms for some time before the development of mental symptoms. The psychoses are therefore, as a rule, the result of a chronic intoxication.

"Some cases of pellagrous insanity appear to belong to the infective exhaustive type of mental diseases, and others rather to the toxic group. In view of the fact that these two groups have

been embraced under the comprehensive term of confusional insanity, many cases of the pellagrous psychoses may better be included under the general heading of confusional insanity.

" It seems to be admitted that the mental condition of pellagrins undergoes an early modification. This early mental state may be ill-defined or show itself by a greater moral impressionability, or greater psychical excitability, or it may be described under the general term of neurasthenia. Later inertia appears, the patients are apathetic and show psycho-motor impediments. There is said to be intellectual hebetude, stupor or even mutism. Thus Lombroso's ' psychical catalepsy ' may appear. If they are not silent, pellagrins respond with difficulty, or have the air of not understanding what is said to them. Insomnia is almost universal and depression (psychic pain) is characteristic. Stupor often ensues, and confusion, the type of exhaustion and intoxication psychoses, dominates the scene. The patients appear frightened, become suspicious, refuse food and medicine, are subject to hallucinations, illusions, delusions, are suicidal (hydromania) and have other criminal tendencies. Episodic disorders of memory and orientation are observed.

" The effort is sometimes made to classify the mental condition of pellagrins as acute and chronic. The *acute* commoner symptoms are: Temperature 39° to 41° C.; neuromuscular excitement, subsulti, contractions, muscular rigidity, exaggerated reflexes, confusion with phases of exaltation, and marked insomnia.

" This condition is more common with alcoholism but may be engrafted upon the so-called chronic form. It is often manifested as an acute collapse-delirium, and is probably the typhoid pellagra (pellagra typhosus) of some writers.

" *In chronic cases:* Depression, confusion, paresthesias, hallucinations, and illusions, memory disturbances, insomnia, exaggerated reflexes, ataxia, and terminal dementia.

" Intermediate forms occur, being marked by alternations of depression and exaltation with remissions and apparent recovery. Excitement may break forth without cause, especially in the spring and summer.

"Polyneuritis is sometimes observed.

"For the chronic form, dementia is the common termination, but it may be complicated by paralysis or tuberculosis.

"In the first attack the pellagra psychosis is an amentia (confusional insanity). In the latter and progressive phase, marked by chronic and incurable cachexia, it is a dementia. It is an intermittent and progressive amentia, which if not cured, or not early fatal, terminates in dementia (Tanzi). Or it may end in chronic mental confusion or in pellagrous pseudo-general paralysis (Regis).

"Depression and confusion are the more common mental symptoms associated with pellagra, but periods of exaltation (excitement) occur episodically.

"Strictly there is no mental symptom-complex characteristic of pellagra, but pellagra may act as the exciting cause of several forms of nervous and mental states, varying from neurasthenia to polyneuritis and meningitis, and from simple depression to paretic conditions and dementia.

"Under the influence of the pellagrous intoxication patients commit crimes — suicide (hydromania), homicide, infanticide, incendiarism, etc.

"According to the degree or duration of the pellagrous intoxication or possibly from idiosyncrasy, the patient is liable to develop the symptoms of acute collapse delirium at any time, and die in the attack.

"It is not unlikely that the mental symptoms of pellagra may differ by seasons or in different countries and in different parts of the same country, just as, broadly speaking, do the physical signs and symptoms of the disease.

"After all, may not Baillarger be right in questioning whether pellagrous poisoning does not, like alcohol, produce these various neuroses and psychoses according to the reaction of different individuals." [1]

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[1] Babcock, J. W.: "The Psychology of Pellagra." *Jour. S. C. Med. Assoc.* Nov., 1910.

CHAPTER VII

DIAGNOSIS

The diagnosis of pellagra is either very simple or else it is attended with great difficulty. When the classical picture is found the diagnosis is not difficult even to one who has never before seen the disease. With symmetrical erythema of the exposed parts of the body, especially of the backs of the hands, the back and lateral aspects of the neck, or the face, less frequently of the feet and lower legs; with a stomatitis sometimes attended with salivation; with diarrhea of varying degree; finally with symptoms of nervous depression or more serious psychic disturbance if the disease has existed for a long enough time — when all of these symptoms are present there can be no chance of error, but it is rather exceptional to find such a case. Many cases whose final history would include this entire enumeration are difficult to diagnose for the reason that these symptoms do not always occur in the regular order which is considered typical. It is no unusual thing to learn on taking the history of a case that the patient has suffered for from one to five springs with sundry digestive disturbances including diarrhea, stomatitis, vague gastric disturbances, and possibly some nervous symptoms before the final outbreak of the typical erythema which made the diagnosis easy. It is this class of cases which presents the great problem of the day in pellagra. It is again a consideration of that condition known as "pellagra-sine-pellagra," or pellagra without skin manifestation. It has been the policy of this work to exclude such a condition, but the fact remains that many of the cases of atypical pellagra — atypical in the time of the appearance of the various manifestations — die because the diagnosis could not be made early enough in the course of the disease to avail anything. One

of the previously recorded cases gave a history of five spring attacks of diarrhea and gastric trouble before the diagnosis was made plain by the appearance of the tardy erythema. I have at this time a patient under my care who has a diarrhea of several weeks' standing which will not respond to any treatment, not even to the use of opium, and in whom the first signs of a stomatitis are just appearing. Last spring the same thing occurred. There is not a trace of erythema, but she is a very old and feeble woman who has been indoors during the trying winter months away from any action of sunlight. I have ordered her placed in the direct sun and hope by this means to prove or disprove the condition as pellagra. If this patient has pellagra valuable time has been lost already, but there were not enough symptoms presented to make a diagnosis without an element of unjustified speculation. We are told that in the London School of Tropical Medicine the diagnosis is made without awaiting the appearance of skin symptoms. In this country at this time we are too inexperienced to undertake such a hazardous thing. This is especially so when we remember that H. F. Harris of Georgia has reported the presence of sprue in the southern states. It has been said in another place that the resemblance of pellagra without skin manifestations to sprue is so great that I have never been able to arrive at any means of making the differentiation. Allen has shown that in amebic dysentery there is another difficulty owing to the presence of a stomatitis in this condition as well as the diarrhea. He has also shown that amebiasis is a very prevalent finding in North Carolina.

There is no place in medicine in which a blood reaction of some sort would be of so great value. At one time I hoped with Tizzoni's strepto-bacillus of pellagra to obtain an agglutination reaction with the blood serum of a pellagrin. After two years I came to the conclusion that this organism was not specific and abandoned any further work. Blood cultures from a patient suffering from a most acute attack or with typhoid pellagra would as often as not remain sterile. I decided that Tizzoni's organism was probably a non-pathogenic form which entered the blood stream through the open wounds of the skin lesion in the acute form

which is usually the so-called moist variety, and that the constancy with which this organism was found was due to the fact that it was one of the inhabitants of the normal skin. This view, however, was purely speculative.

The Noguchi modification of the Wassermann reaction has been thoroughly tested in pellagra by Howard Fox, who reported on thirty cases so examined. His conclusions were important and are here given:

(1) Cases of pellagra do not often give a positive Wassermann reaction.

(2) A positive reaction, when obtained, is generally weak and is easily distinguished from the strong reactions found in syphilis and in many cases of leprosy.

(3) The value of the Wassermann test is not affected by the findings in pellagra.

The value of the Wassermann test while not of direct help in the diagnosis is decidedly useful in the differentiation of pellagra from syphilis, the disease with which it has been most often confused. The reader will recall the case of myelitis which we were unable to decide clinically as syphilitic or pellagrous, especially as the patient attempted to deceive us through his familiarity with pellagra. The Noguchi modification was all that was needed to show a definite syphilitic condition. For years in the southern states pellagra has occurred and many a victim has been done the injustice of a death certificate to this effect when there was not even the history of an exposure. It was called syphilis because it resembled it more than any other disease with which we were familiar. The absence of enlarged glands, the general distribution of the mouth irritation, the appearance of the skin lesions almost exclusively on the exposed portions of the skin surface, the absence of a history or the scar of a chancre, the absence of a history of exposure, the numerous and varied gastro-intestinal symptoms, the more or less characteristic nervous manifestations, and the absence of the generally distributed skin lesions in syphilis would make a differentiation comparatively simple. But it is a well-recognized fact to everyone who has studied medicine for any time that a

patient cannot be trusted to tell the truth regarding syphilis no matter what the consequences of a deception may result in, and for this reason the Noguchi test is a great help.

C. C. Bass of New Orleans has reported sixteen cases of pellagra in which the complement fixation with lecithin as antigen was attempted. Of this number two had syphilis, in one autopsy blood was used, and in another there was found in the blood the æstivo-autumnal parasites, but exclusive of these cases he found a positive reaction in the remaining eight out of twelve. Of this number he said that seven were of the mild type and only one was of the severe type of acute pellagra. In the four negative cases there was a history of severe acute attacks and two were suffering the first attack. He found the reaction positive more frequently in the chronic mild cases and those showing resistance to the disease which, he says, is in keeping with the fact that the complement fixation reaction is due to the presence of antibodies for lipoid substances.[1] "The complement fixation reaction with lipoid substances as antigen has been found in syphilis especially, in certain cases of malaria, in a few cases of scarlet fever, and probably in other diseases. All these, except possibly scarlet fever, are protozoan diseases. The reaction has not been found in bacterial diseases except in rare instances." The writer concluded that deductions could not be drawn from so few cases and withheld any opinion until further work could be done to prove the real value of the procedure in pellagra.

Reference has been made in another place to the finding by the British Pellagra Commission headed by L. W. Sambon[2] of a peculiar body (see microphotograph, p. 98). The victim was a Roumanian girl who had suffered from pellagra for two years. These bodies appear to be invariably located in the nuclear material and were found in the cerebro-spinal fluid, in smears from the sensorio-motor cortex, and from a blood clot lying in contact with and posterior to the lower cervical and upper dorsal regions

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[1] Bass, C. C., "Complement Fixation in Pellagra." Proc. Nat. Pel. Conf., 1910.

[2] *Jour. of Trop. Med. and Hygiene.* London, Dec. 15, 1911. Editorial.

of the spinal cord. It will require further study to determine the importance of this finding in the diagnosis of pellagra, but it is encouraging to know that there is a possibility of some precise means of laboratory diagnosis in these questionable cases.

Recent advance in the study of the etiology of pellagra have had a trend in the direction of an animal parasitic cause and many analogies have been drawn between pellagra and such diseases as trypanosomiasis, kala-azar, and Rocky Mountain fever. This has been especially emphasized by the pathologic findings in pellagra of perivascular round cell infiltration which is so well depicted in trypanosomiasis, and further by the increase in the mononuclear elements of the blood which occurs in both diseases. No such parasite as a trypanosome has ever been found. With the method used by Kock for the detection of the trypanosome in the blood in sleeping sickness I have sought for a parasite of like nature in the blood of pellagra but to no effect. It is to be hoped that this body discovered by Sambon's workers will be proven to have an etiological relation and that we will have some means of determining the diagnosis in atypical cases.

The blood findings in pellagra have theoretically a considerable interest to students of the disease. The increase in lymphocytes has been regarded as characteristic and significant. In the blood report of the Illinois Pellagra Commission [1] we find this reference: "With a normal or slightly increased count (to 10,500) the small lymphocytes were often increased in percentage (up to 50), making a condition of lymphocytosis. Whether this increase of lymphocytes, which is absolute and not relative, has any connection with the involvement of the mucous membrane of the intestine can be only guessed at. It is known that lymphocytes are increased in infections involving the intestines in children and sometimes in adults. In general debility the lymphocytes have been known to be increased. Some such explanation is the probable one in the few cases that presented this phenomenon. Polymorphonuclear basophiles were present in normal number. In general with a count that is approximately normal the differential count is like-

[1] Bulletin of the Illinois State Board of Health. Vol. V, p. 421.

wise so." My own experience is that the blood changes are not so constant and decided as some writers would have them. In many cases other causes may be readily found for the abnormalities. I recall one series of cases in which a very definite cause for the lymphocytosis could be found other than pellagra. The fact that some writers deny the presence of mononuclear increase of the blood is sufficient proof of the unreliability of the evidence of any blood change. If these changes were as decided as the changes found in exophthalmic goitre they would be of great help in the differentiation.

The toxicity of pellagrous blood serum was tested on animals by Camurri,[1] who attempted to find a maize-precipitine, but he found that the toxicity of the blood was inconstant and not to be depended on for diagnostic purposes. In the performance of this test a small quantity of the suspected serum was added to a standard infusion of corn. The mixture was placed at 37° C. for a few hours when, if positive, a precipitate is formed. Camurri determined that this measure had value only in determining that the individual ate corn and that there had been within a short time some lesion of the gastro-intestinal tract. This same observer stated that he found a constant hypoacidity with increase of chlorides in the urine of pellagrins. The combination of these two reactions are counted by him important. Marie[2] expresses it thus: "He concludes that an individual from a section where pellagra is endemic, whose blood shows a positive 'maize-precipitine' reaction, and who for a brief period of time under constant diet shows a urinary hypoacidity with increased chlorides, is a pellagrin in the initial stage of the malady." It is, of course, apparent that these methods are too complicated for general use and can be done only by specially trained laboratory workers.

Merk[3] thought that the skin lesions of pellagra were always sufficient for a diagnosis in the absence even of all other symptoms; that the erythema of pellagra was as distinctive as the eruption

[1] Camurri: Lavinder and Babcock's Trans. of Marie's "La Pellagra," p. 278.
[2] Marie, A., "La Pellagra" and Lavinder and Babcock's Trans.
[3] L. Merk, "Die Hauterscheinungen der Pellagra."

of scarlet fever and measles. This would not be a safe rule unless the application was restricted to one who was very familiar with the variations of the erythematous skin changes. It is not counted wise policy to diagnose scarlet fever without the presence of other symptoms than the scarlet erythema as there are many causes for this class of eruption. My own opinion would be very unsettled unless the child presented the characteristic mouth symptoms. There are certainly very distinctive symptoms of pellagra to be had in the skin. These symptoms have been enumerated at considerable length in another place. The fact remains that doubt often exists in the mind until the patient has been kept under observation for some time. I recall the case of a small boy who had a symmetrical erythema of the backs of his hands which was either sunburn or pellagra. In the absence of any intestinal or mouth symptoms it would not be supposed that there could be much difficulty. The reader must remember the fact that the order of the appearance of symptoms in pellagra is very variable and it might have been such a case under observation. The fact remains that the physician who is a thoroughly trained pellagrologer was in doubt even though the patient was a well-nourished boy living under the very best hygienic surroundings.

G. F. Gaumer [1] of Yucatan distinguishes pellagra from a condition called by him pelagia, which is the result of exposure to the weather and the direct rays of the sun. He also distinguishes it from pseudo-pellagra.

Pellagra	Pseudo-pellagra	Pelagia
In the beginning of the disease patient complains of heat in mouth, throat, and stomach on expiration.	Normal.	Normal.
Sense of taste impaired; there is anorexia and ptyalism.	Normal. Sometimes present.	Normal.

[1] Gaumer, G. F. Trans. Nat. Pel. Cong., 1910.

Pellagra	Pseudo-pellagra	Pelagia
Tongue broad, flabby, and irregularly marked by red blotches.	Uniformly red.	Normal.
Bowels constipated, following diarrhea and sometimes dysentery.	Diarrhea sometimes present.	Normal.
Cuticle assumes a scaly appearance; scales lustrous, thin, and not detachable until disease is far advanced — seldom pigmented; only affects the cuticle.	Dorsal aspect of all affected parts become erythematous, assumes a dark color and are pigmented progressively; scales thick and detachable — epidermis and part of true skin affected.	All exposed parts become erythematous, assume a dark color and covered by large thick laminate scales, detachable. Skin either edematous or hypertrophied.
Pruritus and burning deep-seated, aggravated by scratching. Affected differently by sun and shade.	Superficial, aggravated by sun's rays.	Slight, but the burning is intensely aggravated by sun's rays.
Muscular weakness marked and progressive.	The same.	Normal.
Vertigo, occipital headache, insomnia, neuralgias and cramps.	If present can be traced to alcohol.	Normal.
Ocular phenomena generally present.	If present, alcoholic.	Normal.
The gait is usually paralytic, occasionally paralytic spastic, and progressively ataxic.	Usual symptoms due to alcohol.	Normal.
Mental phenomena progressive from slightest perturbation to complete dementia.	Alcoholic if any.	Normal.
The pellagrin avoids company, seeks solitude, is melancholic, distrustful, etc.	Seeks company, avoids solitude, confiding, cheerful, etc.	Normal. Indifferent.

Pellagra	Pseudo-pellagra	Pelagia
Epileptiform movements rhythmic and often continued to death.	Not rhythmic.	No movements.
Pellagra is not limited to season, age, sex, nor conditions in life.	Limited to alcohol users.	To persons past middle life, who have been much exposed to sun rays.
Attributable to the use of spoilt corn.	To the use of alcohol.	To those exposed to the rays of the sun.
The pellagrin does not fear death, generally unconscious at death.	Fears death and is generally conscious at death.	Indifferent to death.

Pseudo-pellagra, to my notion, is pellagra. This conclusion is based on a study of the recorded cases of pseudo-pellagra and clinically, at least, I do not see any difference. Not recognizing maize as the etiological factor in the production of pellagra the two conditions are at once merged into one.

One of the most troublesome problems that I have had to confront is the differentiation of pellagra and certain weathering conditions on the hands of elderly men. In such cases it becomes necessary to rely on the remaining symptoms. It should be remembered that many victims of pellagra insist that the skin lesions are simply sunburn. I have in mind one of the most typical cases of pellagra in my list. The man was a painter; with the first exposure on a roof in the spring his hands became badly burned. He also had stomatitis, diarrhea, and marked gastric symptoms, together with nervous depression. It was impossible to convince him that the erythema was any other than the result of his exposure to the hot sun. In many cases of diarrhea it has become a habit to examine the hands for signs of an old erythema or for indications of a beginning redness. It is often quite difficult to decide whether the atrophic condition of the skin of the backs of the hands in elderly people is a result of an outbreak of pellagra

or is due to exposure and hard labor. I have at this time a patient with all the symptoms save the erythema, and the examination of her hands reveals a condition which may be due to a former erythema or to the washtub.

A case with photograph is noted (Fig. 30) in order to emphasize the importance of the fact that all symmetrical skin lesions are not pellagra. The child in this case presented a very different history from that of pellagra; there was an absence of stomatitis, diarrhea, and any nervous symptom but the presence of a persistent rise of temperature. The case was carefully studied by E. S. Bullock, to whom I am indebted for an opportunity to see it. There was really no suspicion that the condition was pellagrous, but the occurrence of the lesions on the backs of the hands was very interesting.

Fig. 30. — Lesion which is not Pellagra but Occupies Same Location. (Seen through courtesy of Dr. E. S. Bullock, Wilmington, N. C.)

Isadore Dyer of New Orleans, who has made some of the most important observations on pellagra from the dermatological standpoint, emphasizes the importance of a consideration of the whole course of the skin process. Referring to one of his cases he said: "The photographs are excellent delineations of pellagra—when you know that they were taken of a pellagrin's hand. They would as readily be taken for photographs of a case of blastomycosis, the papillary character of most of the eruption being quite

apparent. Yet the beginning and the course of this eruption on the hands was as typical as it could be in a classic case of pellagra." After a thorough consideration of the other symptoms, which he counted of great importance in the final determination of the disease he added: ". . . It is easily differentiated from vesicular eczema by the persistence of the vesicles, the development of papillary areas, and by the marginate, erythematous, elevated and infiltrated border, all of the latter evidences testifying to a deep-seated affection, beginning deep and not a mere catarrhal process started in the mucous layer." He showed that each of his cases presented types of the disease with points of resemblance to other affections. In all the erythema preceded and at one stage there was nothing to distinguish it from an erythema of the ordinary type and of a simple origin. It was shown that as the group of erythema multiforme is studied its variants have been greatly increased, and included with these are many skin diseases of exudative origin due to many different causes. He thought it was a mistake to consider the erythema of pellagra to be the characteristic symptom especially when it had given place to hyperplastic changes in the skin.

Chronic eczema is the diagnosis under which many cases of pellagra in the past in this country have gone. It is not necessary to go into a lengthy description of the differences in the skin lesions of these two diseases. Suffice it to say that it is only necessary to consider the remaining symptoms when there is occasion for doubt.

One of the most remarkable occurrences in connection with the appearance of pellagra in the United States was the confusion with the skin condition produced by simple burns. This was noted in a report of G. A. Zeller [1] of the Peoria State Hospital. Speaking of the bitter criticism resulting from the universal non-restraint policy adopted by his institution he referred to the biennial report of 1906 thus: "The rush incident to the rapid growth of the institution, when patients were received at the rate of 200 a month, was attended by a fatality in the death of Fred Weber, due to scalds received while being bathed by an incompetent attendant.

[1] Bulletin of the Illinois State Board of Health, Aug., 1909. George A. Zeller, Supt. Peoria State Hospital.

The case was promptly placed in the hands of the coroner, as is every unusual death in this institution, and a searching investigation ordered. The verdict censured the attendant, but charged no criminal neglect." In 1908 there was a repetition of this same note in the records of this institution: "The death of George Wright, who was scalded on the morning of November 25, was directly due to incompetence. He was an untidy and partially paralytic epileptic.

"We maintain two night nurses in our epileptic colony for men, and on the morning in question the nurse on duty while bathing him preparatory to turning her patients over to the day force in a presentable condition, scalded him about the feet. He lived eleven days and died from an intercurrent pneumonia, but the coroner was called as in every other fatality, and the facts placed before him.

"We give three hundred and fifty thousand baths a year in this institution, and the work is performed by expert bathers who are retained for that purpose. In the hospitals and infirmaries the untidy patients are bathed by the nurses, and this patient passed into the hands of an incompetent person who was promptly dismissed." It was stated that the jury was reluctant to accept the scalds as the cause of death. This sad occurrence, which resulted in the discharge of faithful and innocent attendants, is mentioned in the hope that it may be used both as an illustration of the very acute character of certain types of the skin manifestations, and also to emphasize the importance of a very careful consideration of this question of diagnosis.

Acrodynia or the malady of Paris was first noted between 1828 and 1830 in Paris and other parts of France and was described by Chardon. It is mentioned here for the reason that we have learned that there is no such thing as being exempt from any disease. As students we were taught that we need not know anything of pellagra because it did not occur in this country, and in recent years we have learned of the occurrence of many other diseases which were not supposed to be things about which we would ever have to concern ourselves. Most cases of acrodynia, according to Stelwagon,

occur in the East. There are many points of resemblance to pellagra and the diagnosis is not always easy. I feel confident that in the near future it will be found that this disease is occurring in the United States and there is a strong probability that some of the cases diagnosed as pellagra are really acrodynia. The erythema appears on the hands and feet, but is more prone to attack the palms and soles than in pellagra. The disease is not so chronic nor so fatal as pellagra. In acrodynia there is said to be at first marked hyperesthesia of the extremities followed by anesthesia, which is not noted in pellagra. It is thought to closely resemble ergotism as well as pellagra.

It is most interesting to note that Sir Patrick Manson saw fit in his article on trypanosomiasis to differentiate it from pellagra. He said that in pellagra the erythema was characteristic and lacked the ringed or fugitive character of trypanosomiasis. It affected the exposed portions of the skin chiefly, which was not the rule in the latter disease. He further said that pellagra was more chronic and instead of lethargy the mental condition is more on the line of insanity, and finally in pellagra the seasonal variations were distinctive. While for us at this time a consideration of trypanosomiasis seems superfluous, there is no way to tell how long before the disease will present itself even though we have no knowledge of any "fly belts" in this country. The same thing was said of the Simulium, but we note that now many competent observers are finding this little fly in various sections. The comparison is interesting chiefly from the standpoint of classification, as many believe that it is only a question of a short time before pellagra will be classified among diseases of animal parasitic origin and will be separated from the group of grain intoxications.

The most important problem in the diagnosis of pellagra is a consideration of the characteristic psychic manifestations in connection with cases admitted to institutions during the inter-eruptive stage. With symmetrical erythema of the exposed portions of the body in an individual with a depressive mental state there could be no difficulty in arriving at an immediate diagnosis. Unfortunately cases are often first seen after the fading of an insignificant

erythema which has not impressed the caretakers as a matter of any importance, and without at least a history of the erythema the physician would not be justified in making such a diagnosis. For this reason it becomes a matter of the greatest importance to include in the taking of the history of all mental cases a careful consideration of a former symmetrical erythema as well as a history of sundry digestive disorders as stomatitis and diarrhea. Marie differentiated pellagra from alcoholism and paralysis in the last stages chiefly by an absence of marked disturbances of speech. He also noted that the ambitious or melancholy delirium of paralytics is very rare in pellagra. The mental symptoms have been mentioned at sufficient length on another page. The reader will doubtless be impressed with an absence of any distinctive points of differentiation and will conclude that the diagnosis cannot be made of pellagra on the psychic manifestations alone. This brings up the interesting and important point as to whether the pellagrins in our insane institutions are suffering from pellagrous insanity or whether the disease has been engrafted on a preëxisting mental trouble. I notice that the North Carolina Board of Charities reported that in the epileptic colony of that state there were eighteen cases of pellagra. Was the epileptic manifestations a pellagrous manifestation or is it that the mentally deficient are more susceptible to the disease just as are alcoholics? I am of the opinion that many of these patients are suffering from pellagrous insanity, and on the other hand there seems to be no reasonable doubt that the insane of other types are susceptible to the disease. It is not an uncommon thing in the southern insane institutions to find patients who have been inmates for many years and who subsequently develop pellagra.

The reader is to remember the very definite seasonal variation in pellagra which will often of itself clear up a difficult diagnosis. There are very few exceptions to this rule. While the rays of a hot sun are supposed to account for this seasonal appearance it should be remembered that there is more than this, that a patient confined to a room removed from the sunlight will have an outbreak in the spring without any relation to an exposure. It must

also be kept in mind that the time of the outbreaks will depend on the character of the season. In an early season the outbreaks for that year will be correspondingly early, while the reverse is also true. It is often an aid to determine the month of the outbreaks. In pellagra it will be found that the yearly recurrences usually occur in the same month year by year, and by this means the time of an outbreak can usually be accurately predicted.

After the subsidence of the attack the patient in the earlier attacks at least will regain a fairly normal condition, giving the false idea that there has been effected a cure. This is a peculiar property of pellagra and should stand out in bold relief in the history.

It should be repeated that in order to avoid errors in the diagnosis the physician must look minutely into the previous medical history, for in so doing there is great protection from error which otherwise is almost unavoidable.

CHAPTER VIII

PROGNOSIS

From the first writings on the subject down to the present it has always been acknowledged that there was no such thing as a trivial case of pellagra. The earlier writers were disposed to look on it as an incurable condition that inevitably would prove fatal. This view, just as the view of the prognosis of tuberculosis fifty years ago, has undergone many alterations. There can be no more difficult phase of pellagra to discuss than the prognosis because of that remarkable variation of which much has been said which this disease manifests. In one section it manifests certain sectional peculiarities which are not seen in another section. The malignity of the cases which gave the American medical profession their "baptism of fire" with this disease recalls the outbreak of measles in the Fiji Islands as recorded by Osler. In 1875 the disease was imported from Sydney by Her Majesty's Ship *Dido,* and in four months 40,000 out of 150,000 inhabitants died. Osler gives the mortality of measles as from two to three per cent in private practice and in hospitals from six to eight or ten per cent. This tremendous death rate of a disease which cannot be ordinarily counted as a very deadly one, though always serious, is an illustration of a peculiar kind of adaptation where the human organism was called on to combat a new and strange enemy. The same thing was repeated when pellagra appeared in epidemic form for the first time in the United States. Probably never before in the history of medicine in this country has there occurred such an opportunity to study the invasion by a new disease of a race never before affected and to see the wonderful changes brought about in the nature and course of this

disease in a very few years. It is only after five years of observation that we see a condition being approached which resembles the condition of the disease in its own country. It is readily understood why the American physician was loath to accept the diagnosis of pellagra, for there were many points in which the American affection differed from the disease of the Lombardy plains. In Italy the disease is always recognized as a very chronic condition and never acute except as an exacerbation. In the southern states we saw enacted in many cases the changes, which usually would require a decade in Italy, in so many days or little more. It was indeed hard to accept the teaching that this rapidly fatal disease was really the chronic condition which so many Italians endure in secrecy for many years.

The first report of an epidemic of pellagra in the United States was made by George H. Searcy of Tuscaloosa, Alabama, in the *Journal of the American Medical Association* for July 6, 1907. He reported eighty-eight cases occurring in 1906, and of this number fifty-seven or sixty-four per cent died. The disease in this epidemic ran its course usually in from two to three weeks. The acute cases were invariably fatal. In those cases with recovery it was very slow and the patient was very feeble for a long time.

In six cases reported by me[1] in 1909, but which had occurred several years before, there were five deaths, and the sixth passed from observation after recovering from the first outbreak. The first of these died after three attacks; the second, a child, after four attacks in six years; the third, after the third outbreak; the fourth, after only a few weeks acute course; the fifth, after five weeks of an acute course.

The recording of these acute cases opens up an entirely new literature of the disease which, so far, seems to be peculiar to this country, for it is not described by the Italians.

In one house I saw three deaths after an acute course of the disease which never lasted longer than six weeks. Two of these patients, who were children, died suddenly in bed at night and

[1] Wood, E. J., "The Appearance of Pellagra in the United States." Trans. College of Physicians of Phila., 1908, and *Jour. Am. Med. Assoc.*, July 24, 1909.

were so found the next day. At that time status lymphaticus was considered as a cause of death but was not demonstrated. Just what the immediate cause of death was we were never able to say, but the patients died at the height of the attack and certainly of pellagra. Sudden death was not confined to children. I recall the death of a prostitute which occurred in 1905, before we became acquainted with pellagra. She was found dead one morning, and owing to her despondency, which was quite marked, the cause of death was given as suicide from a drug.

The prognostic importance of suicide should be remembered. Pellagrins often commit suicide even when the attack is comparatively trivial. One of my patients was hauled out of a well where she had thrown herself in an effort to suicide. In the American cases the percentage of suicides has been much less than in the European cases.

Soon after the appearance of pellagra, in the same town in which occurred the cases recorded above, I saw six cases in one house without a death. The patients were all under seventeen years of age and none of them at any time were confined to bed. In spite of poor hygienic surroundings the recoveries were prompt and permanent.

It is possible that our earlier fatality was in part due to our ignorance of the real nature of the disease. Since the introduction of the arsenic treatment there has been a material decline in the mortality. It is hardly probable that this was entirely due to the attenuation of the disease, though, of course, it played a part. Pellagra is now being treated intelligently and some hope held out to the patient. It is no longer regarded as an entirely hopeless and incurable affliction. With the earlier diagnosis which a better knowledge of the disease will bring there will be even greater reduction in the death rate.

It cannot be said that the arsenic treatment of pellagra is specific, but it can be said with fairness that in no other disease will it produce such decidedly beneficial results as in pellagra.

It should be recognized in the beginning that the very acute or fulminating type of pellagra is absolutely incurable and that death

is as inevitable as in acute miliary tuberculosis. Fortunately, as stated before, this type of disease is rapidly disappearing and in a few months, probably, will be a mere matter of history. I have not seen such a case in two years or longer.

It is as important a matter to make an early diagnosis of pellagra as it is to recognize tuberculosis in the incipiency. The death rate since the subsidence of the fulminating type will depend directly on the promptness with which the disease is recognized. Unfortunately the medical men in many sections have resented the announcement of the appearance of the disease in their midst and have been loath to diagnose it because, in many instances, they recognize in it a disease which has been occurring in their experience for years and which they have diagnosed differently. Usually this diagnosis has been syphilis. I recall an instance where the medical man refused to make the diagnosis or to institute the treatment because the disease has never been passed on by any eminent dermatologist in his particular section. The hard pioneer work of his colleagues, which was soon checked up by a comparison with the disease in Italy, was discredited. The patient died in a few days of typhoid pellagra in the third year of the disease. There are still many who will not recognize the possibility of the occurrence of this great scourge and, as a result, the patient is allowed to go through the first year without treatment. To attain its highest efficiency treatment must be begun during the first year and anticipatory treatment be instituted in the early months of the second year before the yearly anniversary of the initial outbreak.

At the present time Lavinder [1] estimates that the death rate in the United States is above twenty-five per cent. It has been estimated that in the asylum cases it has reached sixty-seven per cent. It has been pointed out that the estimates in this country are largely based on the returns from the insane institutions, hence they cannot be considered fair for the reason that insane patients are most unfavorable subjects for good results.

[1] "Prevalence of Pellagra," by Babcock and Cutting, W. B., Jr. Senate Document, No. 706.

In the celebrated one hundred cases of the Illinois State Board of Health twenty-two per cent of the cases died, ten per cent were failing, seventeen per cent were improving, and fifty-one per cent recovered. It will be noted on examining this report that in a number of these cases there was sufficient cause for death in diseases exclusive of pellagra.

In the Alabama insane institutions the following results are noted:

The Bryce Hospital since 1896

White men	6
White women	21
Total	27
Deaths	18

Mount Vernon (Colored) Hospital since 1896

Negro men	66
Negro women	144
Total	210
Deaths	121
Average number of white patients	1,350
Average number of colored patients	650

It is interesting to compare the mortality rate of pellagra in America with the European returns.

From Sambon [1] we learn that in 1899 the census returns showed in Italy 72,603 pellagrins with a death rate of 3,836. In 1905 there were 55,029 pellagrins with a death rate of 2,359.

Lombroso, according to Lavinder quoted by Niles,[2] stated that in 1883 in 866 Italian civil hospitals 6,025 pellagrins were treated with 923 deaths; in 1884 there were treated in 993 hospitals 6,944 cases with 780 deaths. This mortality then is about 13 per cent. It will be noted that in the figures of Sambon above the death rate was only little more than 4 per cent. The reader will doubtless be impressed with the extreme variability of returns. There are

[1] Sambon, L. W., Progress Report.

[2] Niles, G. M., "Pellagra: An American Problem," p. 174.

many explanations of this great difference in the various reports and in the various sections from which the returns have come. Reference has been made to sectional variation, and it might be added that there is also a certain variation in the severity of the outbreaks in different years just as there are differences in the malignity of such diseases as influenza in different pandemics.

The occurrence of certain intercurrent diseases does a great deal in shaping the outcome of pellagra. I have already referred to a case with a complication in the shape of a coincidental malarial infection. Certainly in this case the patient's chances of recovery were lessened by this occurrence, if in no other way by a general lowering of resistance. In the southern states the prevalence of many intestinal infections with various parasites is to be seriously considered in arriving at any conclusions regarding the outcome. A large number of pellagrins in the South have heavy hookworm infection and others have heavy infections with the amebæ coli. A case has been mentioned in which the patient passed by anus and mouth during the last two weeks of life about one hundred round worms. Certainly her resistance was lowered and she was less able to stand the pellagra of which she finally died. Tuberculosis acquired during the course of pellagra, which is no unusual thing, or before any symptoms have appeared, materially affects the prognosis. I have lost a patient who was doing well so far as the pellagra was concerned but who died of chronic interstitial nephritis. This occurrence is frequently referred to in the literature as one of the common events. Acute bronchitis and pneumonia often close the scene. Mariani has shown the effects of pellagra in the production of arterio-sclerosis. There is little doubt but that there is such a relation and it has occurred in my experience. It is not improbable that some of our cases of sudden death in pellagrins can be attributed to this cause. Alcoholism is one of the most potent factors in producing unfavorable results in pellagra. This cannot be too strongly emphasized nor is there a known fact about pellagra which is so definite and sure as this. I have been frequently impressed with the possibility of alcohol being a very definite predisposing cause of pellagra, and I

have seen death from pellagra where there could be no doubt but that the drug took away the chance which the victim had for recovery. There is no phase of pellagra which presents such a grave outlook as the complication with alcoholism.

The prognosis in pellagra is directly affected by the improvement of general hygienic conditions. A patient removed from unfavorable surroundings will be much more benefited than by any form of treatment with which I am familiar. I have in mind a case which was removed from his home in South Carolina and carried to a sanatorium in the North for treatment for pellagra. No specific treatment was instituted, but the change and general oversight of his diet and habits were sufficient to bring about what seems to be a complete restoration which is chiefly indicated in great increase in weight and disappearance of all mental symptoms.

Increase in weight is the best prognostic sign with which I am acquainted, and after the subsidence of the usual symptoms of an outbreak I rely on the scales in great measure in estimating the general condition. This increase is of the same importance and significance as increase in tuberculosis.

Pellagra is always counted a feverless disease and in my experience fever never occurs except in case of the coincidental presence of a febrile process as malaria. Lavinder states that fever is a very grave prognostic sign and in this I would agree, but I would also go another step and say that this fever is usually not the fever of pellagra but the fever of some such complication as a mixed bacterial infection through the raw skin surface occurring in the same manner as a like infection in burns. I have never seen fever in pellagra which was not attributable to some very definite cause. This is well illustrated by temperature charts Nos. 1 and 2. In the first the temperature was certainly due to the malarial process; in the second the secondary infection through the raw skin surface produced by the pellagrous process was sufficient to account for the rise, though it is possible that a part, at least, of this fever was an irritative process produced by the remarkable infection with round worms. Any condition, however, which produces fever would be a poor bed-fellow for pellagra and the result would natu-

rally be more serious. My explanation for the unfavorable prognostic importance of fever in pellagra is that, certainly in a large number of the cases, the cause is this secondary infection which does not occur except when the pellagrous lesion is of the moist variety; this would also explain the reason for a larger death rate in cases with this condition of the skin. In my experience one of the most general prognostic signs of value is the character of the skin lesion. The large majority of my cases which were fatal were of this class and it was rather exceptional to see a death in those cases with dry skin lesions. It must not be taken to mean that the prognosis was unfavorable in proportion to the extent of the skin involvement. Many of the comparatively mild cases had that large involvement of the skin which is known as pellagra universalis.

Allbutt [1] stated that when a case reached the asylum stage it was practically beyond recall and that there were few exceptions to this rule. This has not been altogether my experience though mental disturbances must be looked on with gravity. Many of the cases in my experience which have answered the requirements of a cure, that is, have remained well long enough to indicate that there was no longer danger of seasonal recurrence, have been among that number which manifested all symptoms of insanity. With an improvement in the general condition there usually occurs a corresponding improvement in the mental and nervous states. On the other hand mental symptoms usually indicate that the disease has existed for some time and has been making unchecked progress in producing definite organic change. It should be recalled, however, that one of the cases referred to so often on account of the coincidental malarial condition showed definite mental symptoms before the first pellagrous symptom. Another case illustrating this was seen with I. A. Bigger of Rock Hill, South Carolina. The patient had been sick for only a few weeks and had decided symptoms of a grave mental disorder; one of these was mutism and another was a series of motor symptoms. She was sent, through necessity, to an institution in the North for the treat-

[1] Allbutt, "System of Medicine," 1905.

ment of this class of cases. At that time all skin lesions had disappeared and there was left not a remnant of any of the usual pellagrous symptoms so that the physician hesitated about accepting the diagnosis. The result was a cure.

One of the most important phases of the question of prognosis is a consideration of the bearing of the condition known as "pellagra-sine-pellagra." All authorities are agreed that an early diagnosis is almost essential for a favorable result. An early diagnosis cannot be made in cases of pellagra without skin lesions for the reason that these skin symptoms are the pathognomonic sign of the disease. My explanation of this atypical form of pellagra is that there is an absence of the ordinary sequence of symptoms; that the skin lesions are either very late in appearing, or very early before any other symptom, and cleared up before the other symptoms appeared, or these lesions were so trivial as to be overlooked. Every one will recall the case mentioned by J. J. Watson, in which a diagnosis of gastric carcinoma was made, but when the patient was wheeled out into the sunshine the characteristic erythema promptly appeared. I have at this time a patient with a sore mouth and an intractable diarrhea which began as a dysentery. There is a history of the same condition a year ago, but there was then and is now an absence of all skin symptoms though sought for diligently. I have had her wheeled out into the direct sunlight and by this means hope to prove or disprove the presence of pellagra. It is a very important matter in her case to know whether or not she has the disease, because there are reasons why the arsenic treatment should not be used unless actually needed. The contraindication chiefly is the presence of a cirrhotic kidney. The late appearance of the skin lesions in this case, if it be pellagra, will materially influence the outcome.

Subsultus, tremor, retraction of the head, and sundry motor symptoms are counted by many pellagrologers as very unfavorable prognostic indications. Such has always been my experience. These symptoms seem to indicate a grave intoxication which is not usually successfully combated. The most positive indication of the approaching end of the patient is that coarse clonic contraction of

the muscles of the forearms. I have never seen it except in those patients who were in extremis, and I do not recall ever having seen it in any case in which recovery afterwards took place.

Acute exacerbations which are so frequent in pellagra are always attended with a degree of danger. When the condition known as typhoid pellagra supervenes it is recognized that it is in a way a terminal exacerbation and few indeed of the victims ever recover from it. It is in this condition that we so often see the clonic contractions of the muscles of the forearms and other grave motor symptoms.

As in most functional nervous disturbances any operative procedure is usually attended with grave risk to the patient. This risk consists in the precipitation of an exacerbation. I saw recently a case of fatal pellagra in a woman who had been operated on by H. A. Kelly. The procedure which was necessary was immediately followed by an outbreak which was soon fatal. On the other hand, the rest cure attending the recovery from an abdominal section not infrequently acts favorably on the course of pellagra. The preponderance of experience is that as a rule any surgical procedure is apt to produce an acute exacerbation or to light up a latent condition.

It is to be hoped and rather expected that the National Pellagra Conference for 1912 will report that the mortality of pellagra in the United States has settled down to the normal percentage which obtains in Roumania and parts of Italy. This percentage is said to be that of typhoid or about ten per cent. It is very certain that when the initial violence has subsided and what might be called a normal relation of the disease is established the death rate in this country will sink much below that of Roumania or Italy. The reason for this sanguine utterance is that the misery and destitution which is so common among the peasantry of southern Europe is unknown in the United States. Of my certain knowledge there is never occasion for a white man or a negro to want in any section of the southern states and I presume that the same may be said of all sections of the country. The greatest obstacle in the way of lowering the death rate from pellagra in the South is the presence

of hookworm disease, which has done more to retard this section than the war between the States. It is a matter of only a short time, however, before this great resistance lowering agent will be entirely eradicated through the wonderful work of the Rockefeller Commission for the Eradication of Hookworm Disease. Already throughout the South the poor whites have learned the great benefits of this work and are eagerly availing themselves of the opportunities to cast off their lethargy and avail themselves of their pure Anglo-Saxon inheritance. When this great obstacle is removed there will be nothing left to hold them back physically, and they will be able to cope with the scourge which has so cursed the Italian peasantry.

CHAPTER IX

PROPHYLAXIS

A consideration of the question of prophylaxis is approached with a great deal of hesitation because of the fact that anything that may be said on this subject must of necessity be purely speculative. Until the question of the etiology is settled no consideration of prevention could be intelligently discussed. If the attitude of this work was to accept the time-honored maize theory, the matter would be simple and we would at once consider what bad corn is and how to prevent its use. For the sake of completeness and from a purely historical standpoint the literature on this subject will be reviewed.

At this time the Simulium theory of Sambon is by far the most interesting and to many the most reasonable explanation of the etiology of pellagra. If this is finally proven to be a correct view of the cause, what measures can be employed to prevent the disease? The Simulium is abundant in many sections of this country and from my own investigation I am inclined to think that in time it will be shown that this fly occurs in all pellagrous sections. In the case of anopheles in malaria and stegomyia in yellow fever the problem of infection was easily handled by destroying the insect or by screening the patients. The buffalo fly is a field pest and its control would be most difficult if not impossible. The question would arise when does the fly do the biting which infects him; at what stage of the disease can this transmission occur. This would be important, because if the fly is the intermediate host and cannot be controlled it may become necessary to screen the victim to prevent the further spread, and if this is done it must be known for how long a time it will be necessary. On the other hand, it will be argued that as it is a field pest never entering the

house any screening would be superfluous. More must be known about the life history and habits of this fly as well as more evidence to incriminate it before we would be justified in any crusade against an insect that may be harmless.

My colleague, R. H. Bellamy, is at present engaged in a study of a possible relationship between the bedbug and pellagra. He is working on the theory that this insect is an intermediate host. It has been frequently noted by him as well as by many others that this pest is often found in great numbers in the houses of pellagrins, but this does not argue that wherever there are bedbugs there will be pellagra.

Mizell's[1] theory is that pellagra is caused by the consumption of semi-drying oils taken as food. Among these oils he emphasizes cotton-seed oil and takes the stand that this oil, as well as pork fattened on cotton-seed hulls, causes pellagra by some peculiar metabolic process. The recent expression of Zeller's in this connection should be remembered. He said that it was bad policy to condemn a good food on such paltry grounds. I shall always make it a point to use these oils whenever the patient's digestion will bear them in the same way in which I would attempt to improve the nutrition in tuberculosis. In my opinion cotton-seed oil is a very nutritious food and a splendid substitute for lard. It is certain that this product played no part in the pellagra of the time of Casal and Strombio and by the same sign the matter may be dismissed here.

Bayard Cutting, Jr., United States vice-consul at Milan, in writing of the corn theory made this expression:

"The doctrine is, in the present state of science, insusceptible of direct proof and of direct disproof. It cannot be disproved for two reasons: first, because it is impossible to show that any given patient whose food was corn ate only healthy corn, whereas it is easy to demonstrate the presence in spoilt, of a toxic substance. If the corn was well matured, it may have been badly kept, or if

[1] For a consideration of this subject see the *Journal-Record of Medicine.* Atlanta, Vol. XVII, Nos. 5 and 12.

well kept it may have become spoilt after being ground into flour. The flour may have been sound, but have been cooked so badly as to allow decay in the polenta or corn bread. There is always a chance that a man who has eaten corn at all may have eaten spoilt corn. The second reason why the Lombrosian theory is hard to disprove is that cases of pellagrous patients who have never eaten corn are hard to find, and when they are found they can be dismissed as examples of some other disease. The symptoms of pellagra are so varied, even in Italy, that they impinge frequently on those of other maladies. Every province, according to Lombroso, has its own peculiarities; *a fortiori,* we must add, every country. This variety of symptoms allows much latitude to the theorist; in perfect good faith he is able to include as examples of pellagra such cases as suit his preconceived ideas and to reject such as have a contrary tendency.

"Pure zeism, as has been said, is no more capable of direct proof than of direct disproof. Experiments with the poison of spoilt corn have indeed induced serious, and even fatal, results on all kinds of animals, and on some human beings; but they have not induced the precise disease, pellagra. Nor has it been conclusively shown that the poison enters into the human system ready made, and not in the form of a bacterium. And there are no established quantitative relations between the amount of poison absorbed and the progress of the disease. Professor Ceresoli, for instance, experimented on himself for two months, eating every day a large dish of polenta made of the most moldy corn he could find. At the end of two months he had noticed no evil symptoms of any kind. The poison had failed to operate. Why? Probably because in addition to bad polenta, he had eaten good food of other kinds. There must also be a predisposing cause or a debilitating disease, such as typhoid fever, tuberculosis, syphilis, frequent child-bearing, poverty, insanity, or other condition producing exhaustion or lessened powers of resistance. Pellagra appears most easily (if not exclusively) among those whose diet is corn, good or bad; or at least among those who live mainly on corn and other vegetable foods; and among such persons it is probable that a very

small amount of *pellagrozeina,* as Lombroso calls the corn poison, is sufficient to induce the disease.

"Accordingly, among the anti-zeists we meet first with those who call pellagra the disease, not of corn, but of poverty. The corn explanation appears to them not so much false as inadequate. It is true, perhaps, that little or no pellagra is found in places where corn is unknown; but such a concession to zeism appears to them purely formal. Look at the places where pellagra is found. In Spain, where it takes several forms, it appears in districts where corn is either not cultivated or constitutes only a small part of the peasant's diet. In France, the inhabitants of the Landes used to eat corn, but other grains as well, and in far larger quantities. Even in Italy some of the largest corn-growing districts have the least pellagra, or none at all. If in answer to this the Lombrosian says that the districts in question are exempt precisely because their corn is good and does not become moldy, their opponents can point to regions where the crop is exceptionally fine, yet pellagra abundant; and to others, near by, where the corn is bad, and pellagra scarce. No kind of statistical curve can be drawn with corn statistics which has any definite correspondence with the pellagra curve — whether the area of cultivation, the amount of the crop, or its market price be taken as a basis. And then the anti-zeists point to huge corn-fed populations like those of Mexico, Poland, and — till to-day — the United States, where pellagra is entirely unknown. They do not deny that in Italy corn is a cause of pellagra; but the cause they find in the inadequate nutrition and poverty of the peasant, who is enfeebled during the long winter months by an inadequate vegetable diet, and whose debility takes a violent and specific form when the labor of the spring begins.

"The poverty theory is almost too indefinite to criticize; it is itself little more than a criticism." He says further: "To tell a peasant not to eat corn is about as practical as to tell him to be rich, but to prevent him from eating a certain diseased part of the corn, and to advise him to harvest and store it in a certain manner, in order that it may not become diseased, does not exceed the bounds of possibility."

In Italy the problem of preventing the people from eating diseased corn is one which holds an important place in the affairs of the nation. It is considered there to be a problem entirely of prophylaxis rather than of cure. The whole attention is directed toward the improvement of living conditions among the rural and agricultural population. It is counted most important to exclude moldy corn and its products from the diet of these people. The Italians further claim that no good remedy has been found except a radical change of food. The crusade along this dietetic line was begun by Joseph II of Austria who gave all his influence and aid towards the measures for the control of this great scourge. The hospital founded by him was the one in which Gaetano Strombio, the elder, made his fame. Cutting further said:

" The first serious attempt, in Italy, to deal with pellagra, was in 1879, ten years after Lombroso's famous essays. A census was taken of the pellagrous patients in Italy, and as a result of the census a bill was introduced for the regulation of corn cultivation and importation, and the establishment of public desiccating machines. The bill failed and the only immediate result of the census was an annual grant of 36,000 lire ($5,790) from the government toward the relief of pellagra — about six cents for each patient. This amount was raised at a later date until it amounted to 70,000 lire ($13,510) in 1899; and under the law of 1902 100,000 lire are contributed annually for the prevention and cure of pellagra, and as much more for the introduction of improved methods of agriculture. The census of 1879 was an epoch-making event. It brought home to the people as a whole the gravity of the situation, and it stimulated the various provincial governments to act independently. Many provinces appointed pellagrological commissions, took censuses, and founded hospitals, or *locande sanitarie.* From 1879 to 1903 was a period of local and provincial activity. The conclusions of doctors were tested on a small scale, and the way prepared for general legislation. Meanwhile, in 1895, the Crispi administration had issued an ordinance forbidding the importation of spoilt corn, and providing for inspec-

tion at the chief ports. In 1902 the 'Law for the Prevention and Cure of Pellagra' was passed, and in the following year was issued the regulations for the enforcement of the law. Since that time four years have elapsed, and already pellagra may be said to be a doomed disease. The statistics, so hard to interpret as regard particular details, bear unmistakable testimony to a general decline in the disease under the operation of the law.

"The main provisions of the law are as follows:

"(1) Absolute prohibition of the importation, sale, holding for sale, or grinding of spoiled corn or products of corn destined for human food. If the corn is destined to feed animals or to be used for other purposes, it is admitted only by special permit of the prefect.

"(2) Obligation upon all communes to report cases of pellagra. A commune with several cases is declared pellagrous, and falls under the following provisions:

"I. Government inspection of all corn dried, stored, and consumed in the commune.

"II. Obligation on the part of commune and province to es tablish public desiccating plants, to provide curative nourishment for all patients, to provide patients and their families with free salt, and to treat severe cases in special institutions.

"III. Establishment of pellagrological commissions in all provinces affected with the disease.

"IV. Assignment of a government grant of 200,000 lire annually and obligation upon provinces and communes to defray, in equal portions, the expenses entailed by the act."

He says further, commenting on these provisions:

"This is the charter under which the struggle against pellagra is now being carried on. It proposes to examine the several dispositions of the act; then to give some details in regard to certain provinces which the writer has been able to investigate in person, and finally to append such statistical data as will give an idea of present conditions in Italy as a whole.

"The dispositions of the act are of two kinds, curative and preventive. The curative measures, which may be examined first, fall into several classes, distribution of salt, administration of food, either at the patient's home or at sanitary stations (*locande sanitarie*), treatment of severe cases in hospitals, pellagrous hospitals (*pellagrosari*) and insane asylums. The prophylactic measures are most numerous. Those to be chiefly noted are: The testing of corn and flour brought in at the frontier or offered for sale or brought to the mill, the exchange of bad corn for good, desiccating plants, cheap coöperative kitchens, the improvement of agricultural methods, and the instruction of the people as to the danger of bad corn."

A plentiful supply of salt is thought by the Italian government to have a tendency to counteract the bad effects of a corn diet. Seventeen and a half pounds for an adult and eleven pounds for a child is the yearly allowance of the government.

According to Cutting, the amount of salt distributed gratuitously from 1904 to 1907 is as follows:

1904–5	1,953,469 lbs.
1905–6	2,520,553 lbs.
1906–7	3,118,628 lbs.

The law of 1902 makes a curative diet for the indigent victims of the disease obligatory on the part of the government. Two periods of at least forty days per annum in which this prescribed diet was required was the specification of the provincial pellagrological commission. The distribution is made from house to house, by the use of economic kitchens, and by sanitary stations.

In certain provinces where the disease is thought to be under control the distribution is made to families through the communal authorities. No special instruction is thought necessary in such cases.

The economic kitchens supply sound food to the rural population at small cost. These kitchens are the property of the communes and sometimes of charitable organizations. Sometimes these

kitchens are made use of to supply the free food when there is no *locanda* or sanitary station near by. Cutting says that in 1906 there were one hundred and seventy-one of these kitchens in Italy, and in 1907 the number had grown to one hundred and eighty-seven.

The sanitary stations (*locande sanitarie*) are an improvement on the cheap kitchen. The first station was established in Bergamo in 1884. To these stations the pellagrous patients come once or twice a day and receive suitable food, which they eat on the spot. This food consists of soup, bread, meat, and wine, with a certain amount of cheese and vegetables. It is hoped by this means to build up the underfed pellagrin and thereby increase his resistance. The time selected for this treatment is the spring and autumn when the outbreaks of pellagra are expected.

While the *locanda* has been the subject of criticism, it is claimed that they accomplish a great good in retarding the progress of advanced cases and effecting a cure in many incipient cases. It is claimed that eighty per cent of the patients go away distinctly improved. The usefulness seems to be in direct proportion to the length of time the institution is run each year. It is further claimed that the provinces which have been most successful in controlling pellagra are those well supplied with these *locanda*. The provinces of Bergamo and Brescia are examples of the good accomplished by an abundance of *locanda* run a sufficiently long period.

There are twenty-two special hospitals or *pellagrosari* in Italy for the care of the pellagrous. These institutions care for the cases too far advanced for the dispensary plan of treatment. The plan adopted by them is described as dietary, balneary, and medicinal. The dietary plan is about the same as in the *locanda*. The medicinal treatment embraces numerous baths, as sulphurous, ferruginous, arsenical, and saline. These hospitals are supported by the government and by private subscription. Some of these institutions, as the one at Inzago which was visited by Cutting, limit their cases to a certain period of life and to a certain stage of the disease, because their mission, even in this class of institutions,

is understood to mean prevention, and it is hoped to effect this by taking the young (in this case between twelve and twenty years) and preparing them for life. It is probable in the natural course of events that in this country at no very distant time it will become necessary to make some such provision as this for the care of our own cases. When that time comes it is to be hoped that this experience of Mr. Cutting will be held in mind. He said about this institution at Inzago:

" The effort of Director Cav. Giuseppe Friz is to secure the children of pellagrous patients, and to take them into the hospital the moment the first signs of pellagra appear. The statistics of the hospital are admirably kept. Every detail in regard to a patient's past history, to his family, to the diet to which he is accustomed, and to his precise symptoms, are carefully registered at the time of his admission. His weight is then taken and his strength tested. During his stay a record is kept of his diet, of the medicinal cure administered, and of the results upon his system. Finally a systematic effort is made to record his history after leaving the hospital."

It is more and more the policy of the Italians to remove from the villages the pellagrous insane to the insane institutions where special treatment is provided. It is a well-recognized fact that Italy is second to no other country in the character of their care of the insane, as well as their skill as psychiatrists.

Cutting says that the provisions of the laws of 1902 and 1903 are adequate to protect the people from bad corn brought from abroad. The suspected cargoes are examined by experts and when the corn is condemned it is sent to the distillery or else is denatured. The tests for spoilt corn have been mentioned on another page. It is said that such indications as mildew or the odor of mold are sufficient proof of its unwholesomeness, but it is further emphasized that these may be corrected by drying in the sun, so that their absence is of no importance.

" But the peasant should be warned against any corn that is cov-

ered with dust, that is, damp to the touch, or that gives forth any smell of mold when warmed in the palm of the hand. He should be on his guard against corn of a pale color with a dull surface." (Cutting.)

It has been pointed out that the inspection of corn on the frontiers is comparatively easy, but at the mills or in the markets, especially when in the form of meal, makes a much more difficult problem. The government ownership of grist mills would be necessary in order to control the adulteration of meal, thinks Cutting. This plan is strongly advocated by the Italian pellagrologers.

Cattedre ambulanti are institutions of an educational character in Italy which disseminate exact knowledge of agriculture to the farmers. They coöperate with the health authorities in encouraging the farmer to abandon the objectionable forms of maize. For example, the much-dreaded *quarantino* is shown to be a poor crop, and a form of maize which requires a longer time for maturity is advocated. This objectionable grain is being abandoned in many sections. The peasant is taught to plant the *Mathilde* potato in place of both *quarantino* and *cinquantino*. Cutting found many evidences of the presence of an excess of pellagra in those provinces where *quarantino* is still generally grown.

The artificial drying of maize is a new departure in Italy. It has largely supplanted the more primitive methods of hanging the ears of maize on the rafters or drying frames in the houses of the peasants. In some instances the grain was dried in the open air. The fault lay in storing the corn in poorly ventilated, dirty places. Cutting says:

"If Italy is the home of pellagra, while Mexico and Burgundy are entirely free from the scourge, the difference may be due simply to the fact that in Mexico and Burgundy corn is fired almost as soon as harvested. Artificial desiccation is the most important of all prophylactic measures against pellagra. It has objections, however, to encounter from the peasantry. The corn loses weight,

they say. This is true; but the weight lost from decay is greater. It will not germinate. This is true likewise, if the desiccation is not properly performed; but the best desiccators leave the corn with all its natural properties unimpaired. It is expensive. Not so expensive, on the whole, as the outdoor frames. The best desiccator yet contrived, that of Pietro Cattaneo, dries 110 pounds of corn with a fuel consumption of 1 per cent. Nevertheless, in order to remove, as far as possible, the objection of expense, the law of 1902 provides that every family may dry at the public desiccator, free of charge, so much corn as is required for the household needs. Further use of the desiccator must be paid for, but at rates which allow nothing for profit.

" Desiccators are of two types, — fixed and portable. The portable type has the great advantage of saving the cost of transportation of the corn. It can be carried in sections and set up in the middle of the corn belt. It is cheap enough to be within the means of peasants. The fixed type, however, is infinitely preferable. The air is kept at an even temperature and circulates equally in all parts of the machine; thus none of the corn is spoiled or deprived of any of its properties. A pamphlet describing the Cattaneo desiccator is enclosed. Air heated by a furnace is forced by a ventilator into a chamber of seven stories. Each story is a circular revolving wire tray, containing about 1,390 pounds of corn. The top tray is filled from above. After a certain time its contents are emptied by pressing a lever into the tray below in such a way that they are thoroughly remixed. The corn thus passes gradually to the bottom tray, whence it goes to a receptacle, where it is cooled by means of a ventilator, and thence out of the machine by an incline plane. The first tray load of corn takes seven hours to pass through the machine; after that 1,400 pounds come out each hour. The cost of the machine is about $540 and the power required to run it about 2½ horse power. Larger machines of the same kind, costing about $1,840, have a daily capacity of 88,000 pounds and require an engine of 8 horse power. In the Cattaneo desiccator the air is forced through

the trays in both an upward and a downward direction; the air which absorbed dampness from the corn is replaced constantly by dry air; the temperature is kept low (about 104° F.) with economy of fuel and without risk of injuring the corn; and the mechanism is so simple that the machine can be handled by any laborer of ordinary intelligence."

The use of the public desiccator for moldy corn is avoided because a temperature sufficient to be effective under such conditions would burn up the grain. In 1904 there were 179 public desiccators; in 1905, 221; in 1906, 389, and in 1907, 461. In 1907 there was desiccated 54,747,000 pounds of corn.

The law of 1902, about which much has been said, gave the power to the commune to establish public storehouses for the grain of the peasantry who could not supply suitable accommodation for their maize. Owing to the cost this has not yet been accomplished, but the advantage is immediately appreciated. The storing of the grain in the dark, ill-ventilated huts of the peasantry could be nothing but unhygienic, and a prevention of this evil is devoutly desired.

The establishment of rural bakeries has done much to do away with the use of maize as a food in northern Italy, and the substitution of wheat and other foods in its place. It is predicted that it will not be long before maize will cease to be an article of diet in Italy altogether.

Ceresoli introduced the plan of exchanging good maize for the inferior qualities of the peasant, giving in return a smaller amount of good grain. While this plan was found not to be very expensive and to meet the approval of the pellagrologers, it has not been successful.

None of these measures could be objected to, even by the most pronounced antizeist. It is evident that maize, owing to its large amount of fat and its very poorly protected embryo, as well as its water content, is very subject to deterioration and is therefore easily rendered unwholesome, to say the least. Any measure look-

ing to a protection of the grain from any form of decomposition must appeal to the mind without regard to any consideration of the possible relationship to pellagra. It has been shown that in this country bad corn is to be found on the market, and we know that some has already been condemned by government officials. As before stated, the question of water transportation can be passed over, as practically no corn is shipped in this way in this country. The shipping of corn from the western states to the southern states should be considered. It is not infrequent that a carload of corn is refused by the local dealer because of the "heating" process which has occurred in transit. This detection seems to require no skill. What becomes of this "heated corn"? It is supposed to be sold for such purposes as the feeding of poultry, but it is questionable if this is always the use to which it is put. There should, of course, be a more rigid supervision of this corn, as well as a more rigid inspection of all corn. It is hardly probable that the trouble in the United States is with the quality of corn raised. If there has been any change it would seem that such a change would be for the improvement of the grain. Certainly the farmer has been well instructed lately regarding the growth of what has been called "the great American cereal."

Alsberg,[1] after considering the methods of cultivation of corn in this country and finding nothing there to account for pellagra, then considers the fact that in the last eight or more years the climatic conditions have somewhat changed. He shows that we have had a preponderance of cold wet falls and late springs. He emphasizes the importance of the Indian summer to produce the best grade of corn. As this weather has been lacking in late years, the corn has been harvested in an unripe condition. He thinks that the outbreak of pellagra at this time is a most significant coincidence. He shows that there is a tendency for the extension of the corn belt farther to the north and the west because the wheat lands of the northwest are not so productive as

[1] Alsberg, C. L., "Agricultural Aspects of the Pellagra Problem in the United States." *N. Y. Med. Jour.*, July 10, 1909.

they were. It is possible that the limits of safe corn cultivation have been exceeded.

It is said that more corn has been harvested in this country before it was entirely ripe than formerly. Owing to this extension northward and also to the changing season corn is not thoroughly hardened and dried before the harvest, according to Alsberg. The moisture content of corn being greater than of any other grain, it is all the more difficult to prevent molding. It is shown that even ripe corn imperfectly dried is subject to mold. This imperfectly dried corn, possibly unripe, does not spoil during cold weather, but with the coming of the warm season.

Alsberg says:

"Corn is transported in closed cars without ventilation. The grain of corn is a live thing. It is breathing, consuming oxygen, giving off carbonic acid, and as the result of its respiration, heat. The heat thus given off increases the rate of respiration till the corn heats up hot enough to create ideal conditions of temperature and moisture for the growth of fungi. Corn transported thus into the northeast may have its tendency to ferment checked by the colder climate. Corn shipped to the South will on the contrary have the tendency to ferment augmented often by the warm moist climate. Quite in conformity with this fact, is the experience of the United States Department of Agriculture with shiploads of corn exported from the seaports of the two sections to foreign lands. Shipments from the north Atlantic ports are not so apt to become spoiled; as we go South more difficulty is experienced; while the greatest difficulty is often encountered with shipments from Gulf ports. . . . The remedy then is to cause the corn to be thoroughly dried before transportation. To bring this about, corn must be sold on a basis of its moisture content. But to make this possible there must be an efficient impartial system of grain standardization. Such a system under the complex conditions of our present civilization can, without doubt, be best carried out by the Federal Government. Federal grain standardization would not merely tend to restore to us our lost markets,

it would not merely increase our economic efficiency, it would not merely make for higher business morals and greater commercial honesty, but it would also be a most important public health measure. Such legislation would be as truly a potent influence in our public health as a Federal quarantine."

CHAPTER X

TREATMENT

Until we have a solution of the question of the etiology of pellagra the consideration of treatment must be, in a measure at least, unsatisfactory. In the United States there is a growing dissatisfaction regarding the accepted theory of the etiology. There are many, and the number seems to be steadily increasing, who will not accept the damaged maize theory. This same condition of things is found in England. It is significant that at the meeting of the London Society of Tropical Medicine and Hygiene in December, 1911, the work being done by Sambon and his followers was endorsed, and it was officially announced that the society rejected the maize theory.[1] Could we accept the maize theory this chapter would resolve itself into a consideration of an improvement in grain conditions. As this theory cannot be accepted and as the evidence in favor of Sambon's hypothesis grows day by day, we must look at the all-important question of treatment from all standpoints.

Certainly there can be no consideration in medicine in this country at this time of any greater importance. Last year E. H. Martin [2] estimated that there were 100,000 cases of pellagra in the United States and predicted half a million for the year 1912. Such figures call for the gravest consideration, and as at this time our efforts along the line of prophylaxis are pitifully wanting in effectiveness, it behooves the whole profession to give greater heed to the question of treatment in the hope that some specific

[1] *Jour. Soc. Trop. Med. and Hygiene*, Dec. 11, 1911.

[2] Martin, E. H., "The Arylarsonates in the Treatment of Pellagra." Read before 27th Annual Session Tristate Med. Soc. (Miss., Ark., and Tenn.), Nov., 1910.

may be found. It is encouraging to recall that a specific was used for syphilis many years before a determination of the etiology.

The drugs which have been tried in the treatment of pellagra are countless. It is a notable fact, however, that only those remedies containing arsenic in some form have stood the test of time. Coletti and Perugini were the first to employ this drug in the treatment of pellagra, and this treatment was revived and given new impetus by Lombroso, who also claimed that the same benefits could be derived from the use of sodium chloride. This latter drug was found to be badly borne by the stomach and consequently never became popular, except in so far that provision was made by the Italian government to provide salt for the sufferers. Salt is a government monopoly in Italy and the price is often too high for the purse of the poor peasant. During the years 1906 and 1907 the Italian government distributed 3,000,000 pounds of salt.

Among the drugs prominently advocated is quinine by Isadore Dyer[1] of New Orleans. His justification for this treatment is thus expressed:

"For years I have treated all types of toxic erythemas where the specific cause was not determined with quinine and salicylic acid salts. The success arrived at made me give quinine in the first case, and I have continued to use this as the mainstay in each case of pellagra that I have had to treat, or for which I have advised treatment. In each case the symptoms were promptly controlled with quinine (given usually as the hydrobromate) in good-sized doses and by keeping up the quinine continuously. In two cases the symptoms have disappeared entirely. In two last cases the treatment has not been followed long enough to establish a definite report, but each case has improved enough to make the prognosis favorable. I have no argument to make for quinine, as I have used it with empyric judgment and have continued its use because the results have been good — so far."

[1] Trans. Nat. Pel. Cong., 1910.

I have obtained no results from quinine, except in those cases with a coincident malaria. As pellagra and malaria occur in the same parts of the country, it is no unusual thing to find a complication of malaria, and in such cases, of course, quinine influences the course of the illness favorably.

W. S. Thayer gave one case thyroid gland with good result, but this experience has not been repeated, as far as can be determined by the literature.

It is important at the outset of a consideration of this subject to decide just what the criterion of a cure shall be. Many writers have claimed great things for sundry therapeutic measures when their observations were based on one year's experience. Any remedy will be likely to be accounted a specific under such a test, for the disease process will subside in the course of a few weeks, in the majority of early outbreaks, under any form of treatment. It cannot be said that pellagra is a self-limiting disease, for it will recur year after year unless curative measures are adopted, but it can be said the pellagra outbreak will subside without treatment unless the attack is sufficiently severe to cause death. As a rule the disease does not come under observation until the outbreak is well advanced and often not until near the end. If the inexperienced observer applies a remedy in such cases and, because the patient recovers from the attack, assumes that the drug was the cause of the recovery, he has fallen into an error which will be proven by a recurrence during the following spring. This source of error accounts, in a large measure, for the large number of drugs which from time to time have been vaunted as specifics. A patient who has been under treatment for pellagra should not be counted recovered until two years have elapsed without any recurrence. It is unknown in my experience to see a case which has passed two years suffer a recurrence, but it is no rare thing to see a patient escape one attack and have a recurrence the next year. This two-year rule is as important as the five-year rule for the recurrence of carcinoma. It is important also, having this rule in mind, to keep pellagrins under treatment as long as leutics. It is only fair that these people should be

told that their disease will require three years of treatment and to enjoin on them their responsibility in coöperating with the physician. Many cases have recurred in my experience because the patient failed to obey the instructions regarding the time of returning for the anticipatory treatment. After all symptoms of an outbreak have well subsided it is my custom to abandon the arsenic treatment until a time which is one month earlier than the month in which the original outbreak occurred. For example, as the month of March is often the time of the outbreak in my section I have my patients come early in February and receive one month of vigorous treatment — just as vigorous as the treatment of the outbreak. If this rule is strictly adhered to the recurrences in the majority of cases will be prevented.

As the idea of the protozoal origin of pellagra has grown in favor, the use of arsenic has been more generally resorted to in the hope that it would have the effect that it was found to have in trypanosomiasis. One of the main arguments in favor of an animal parasitic origin of pellagra was that these arsenic derivatives had such a decidedly favorable effect. Since the introduction of this form of treatment the whole aspect of the medical profession towards this dread disease has undergone a tremendous change. In the United States the first cases of pellagra were of the fulminating type and none recovered, in spite of treatment with atoxyl and soamin. It has been said that the prognosis in this class of cases was as unfavorable as the prognosis in acute miliary tuberculosis, and an analogy may be drawn between these two diseases in regard to treatment. It has been proven that tuberculosis is one of the most amenable diseases to treatment, provided it is recognized early enough. Just so with pellagra, when the ordinary type is detected early and active treatment instituted, there is no reason why the prognosis should not be as favorable as the prognosis of tuberculosis under the same conditions. Certainly such has been my experience, with the exception that in children pellagra is a comparatively trivial disease, as a rule.

Babes [1] in Roumania was the first to suggest the use of atoxyl in the treatment of pellagra. But the drug at that time was by no means new. It is a difficult matter to find anything about atoxyl in English medical literature, so at this point it will be mentioned at some length, taking it as a type of the arylarsonates. My own experience has been limited exclusively to the use of atoxyl, as it has been entirely satisfactory, but I am now instituting the use of soamin in my hospital cases on the strength of the favorable experience of Babcock of South Carolina and E. H. Martin [2] of Hot Springs. The only reason for this trial of soamin is that it is said to be less toxic.

Georgopulos [3] says that Bertheim found atoxyl to be the paramidophenylarsenate of sodium, containing 24.1 per cent of arsenic and not the metarsenanalid ($C_6H_5NHAsO_3$), containing 37.69 per cent. It was found to have an elective action on the blood, the skin, the nervous system. Thomas of Liverpool was the first to use it in diseases of protozoal origin. It was employed experimentally in the treatment of the trypanosome of surra, nagana, and sleeping sickness, using for the experimentation rats, mice, and rabbits. The results of Mesnil and Nicolle were not very encouraging. The healing action of atoxyl in trypanosomiasis was first demonstrated by Robert Koch in a large number of cases. Uhlenhuth, Gross, and Bickel found atoxyl not only a healing, but also a preventive agent in experimentally produced *Dourinekrankheit*, whose cause is a trypanosome. The great importance of the study of atoxyl consists in acquaintance with the varied manifestations of toxicity. The dose of the drug was supposed to be about one-third of a grain before its use in pellagra, but to-day it is being given hypodermically in as much as seven and a half grains (0.5 grams). This dose has been known to produce such symptoms as chills, fainting, headache, blindness from retro-

[1] Babes, A., "Tratumental Pelagerei cu boluri de carna cruda." *Spitalul, Bucuresci*, 1901, XXI.

[2] "The Specific Treatment of Pellagra," by E. H. Martin. Read before Med. Soc. of Southwest, October, 1911.

[3] Georgopulos, "Die Behandlung der Malaria mit Atoxyl." *Munch. Med. Wochr.*, March, 1908.

bulbar neuritis, colic, loss of appetite, insomnia, albuminuria and the presence of casts in the urine, red and white blood cells in the urine, vomiting, dryness of the throat, retention of urine, fever, and cough. Often symptoms of a profound intoxication are manifested in vomiting, pain in the stomach, nephritis, and retinal hemorrhage. It was found by Blumenthal [1] on the rabbit that thirty hours after the administration of atoxyl arsenic could be recovered from the urine. The greatest amount of arsenic was found in the blood in from two to four hours after administration. This same writer, in spite of the warning of the danger which sometimes attends its use, began the treatment of malaria with seven and a half grains (0.5 grams), given by hypodermic every day for three days; then the same amount every other day, and finally with three days between the doses. In this way the patient received in eighteen days sixty-seven and a half grains (4.5 grams), which is more than we usually give in one season to the severe cases of pellagra. Many evidences of the danger of the drug, especially in regard to the eyes, are to be found in the literature, and these will be mentioned at some length. It is only fair to say that I have never seen any untoward effects from the use of atoxyl except in one case, where the symptoms of acute arsenical poisoning were produced, but later this same patient was given the maximum dosage repeatedly without any repetition of these symptoms, which has led me to suspect that in the first instance the hypodermic injection was prepared with very hot water and we are taught that hot water will decompose the drug. It must be prepared with the strictest attention to asepsis, but without any heat. It has been shown by W. Jakimow that light does more to decompose the solution of atoxyl than does a high degree of heat. For this reason the hypodermic tablets which were for a while prepared for the American trade were a great aid in avoiding decomposition. It is unfortunate that the manufacturers have seen fit to withdraw this product of one-grain tablets from the market. At this time the only tablets on the market are the one-third grain, the use of which when the dose

[1] *Munch. Med. Wochr.*, 1907.

is from six to seven and a half grains, is absurd. An effort is now being made to have the solution dispensed in ampoules containing six grains or possibly a little more, using a dark colored glass. Unless this is done it would be preferable to abandon the use of this drug and substitute soamin. It should be an unvarying rule either to give atoxyl in large doses or not at all. It is, therefore, all the more necessary to watch the patient with great care. It is never wise to give this treatment unless the attending physician is competent to make ophthalmoscopic examinations, and it is far better to have the patient where this can be done by a skilled oculist. Even in blindness from the use of atoxyl the eye changes are difficult to find in many cases, therefore the most skillful and painstaking examinations are indicated. Of course with the first eye symptom the treatment should be abandoned. It is also necessary to watch the urine, for the reason that the drug has been found at times to produce very decided kidney irritation, which may amount to a permanent change. It is my custom to have a competent oculist watch the eyes in my cases of pellagra, but he has never had occasion to call a halt in the treatment. I have used the drug in a large number of cases and have reports of equally as many cases among my medical friends throughout North Carolina and never yet have we had any untoward results, though they have been expected and looked for. It is possible that our favorable experience has been due to the fact that the drug is very carefully prepared for use without heat and that the intervals between treatment are made longer than the European plan. We usually give from five to seven grains every fourth day in the beginning and later increase the length of the interval. The results have been so gratifying that the disease is no longer dreaded as in the beginning of our experience. In North Carolina atoxyl has been very largely employed and the results are almost invariably favorable. When first used the dosage was too small to produce any favorable effect and hence the unfavorable reports at that time; then, too, the disease was of the fulminating type which would not respond to any form of treatment.

Koch [1] found that in sleeping sickness atoxyl produced splendid results, but he reported twenty-two cases of blindness, which was one and a half per cent of the cases observed. The ophthalmoscope did not show any changes and the optic nerve was not affected, as far as could be determined. Nonne objected to the name of atoxyl, because it was a very toxic substance, producing blindness in six of his cases. He said that it produced a descending neuritis. In one of his autopsies was found a parenchymatous degeneration of the fibers of the optic nerve. Igersheimer [2] did some important experimental work on the effects of atoxyl on the eye of the rabbit and also the effects of the use of the drug hypodermically in dogs and cats. Injections into the anterior chamber produced no pathologic changes. The injection of one milligram into the crystalline lens produced severe macroscopic and microscopic changes. The direct contact produced a necrotic effect on the nervous elements of the retina. In the dog very few general symptoms were produced, but in the cat a very interesting group of symptoms resulted. Among these symptoms were slowness of movement, ataxia, spasms, spastic parapareses, and in the eyes there often appeared conjunctivitis as well as other optic nerve and retinal changes.

Babes in Roumania was the first to use atoxyl in the treatment of pellagra. Later Babes, Veseliu, and Georghus [3] treated a series of cases by the hypodermic injection of 0.5 grams of atoxyl, employing at the same time an inunction of five grams of a one-to-fifty preparation of arsenic trioxide in lanolin, and by the mouth administration of three-fiftieths of a grain of arsenic trioxide in one day. This treatment was repeated at varying intervals, depending on the individual needs of the case. The results were most gratifying, and there were no untoward effects. I recall a case in which this treatment was used without modification. The case was considered hopeless, but two years have elapsed and the

[1] Koch, "Schädliche Folgen der Atoxylbehandlung." *Deutsche Med. Wochr.*, 1907, No. 46.

[2] Igersheimer, "Exper. Stud. ueber die Wirkung des Atoxyl." *Munch. Med. Wochr.*, 22 Sept., 1908.

[3] Babes, Veseliu, and Georghus, *Berlin, klin. Wochr.*, Jan. 8, 1908.

man is at his usual labor. He lost only one week from his work, as all of his symptoms which were at the height at the time of treatment rapidly subsided. It is not usual that such heroic treatment is necessary. Usually from five to seven and a half grains (0.35 to 0.5 grams) is a sufficiently large dose. At the beginning of the treatment the interval between doses is four days, but this is gradually lengthened as improvement becomes established. The drug should never be administered by the mouth, as it is decomposed by the acid gastric juice.

It was a notable fact that the end results of atoxyl treatment were often delayed. It was no uncommon thing to send out of the hospital as unimproved and incurable cases of pellagra which subsequently, without any further treatment, made good recoveries. The histories and later course of these cases would indicate that this treatment was not merely of benefit temporarily, but also permanently. The following case illustrates the usual results obtained by this treatment.

C. P. White. Age, 60. Came under observation in July, 1910. He was emaciated and his weight was 95 pounds, though his usual weight was about 160. He was a painter, but for three years had been forced to abandon his work. In addition to weakness and emaciation he was suffering from a profuse diarrhea, having from twelve to twenty movements daily, and also a catarrhal stomatitis with some salivation. On the backs of his hands there was found the typical erythema of the moist variety with a number of large blebs. He was melancholy and at times emotional. All reflexes were increased.

On every fourth day he was given hypodermically 0.33 grams (5 grains) of atoxyl and on intervening days an ampoule of the arsenite of iron, which represented one-seventieth of a grain of arsenic trioxide. This was administered in the same manner as the atoxyl. For months his diet had been greatly restricted and when these notes were made he was eating only soda biscuits and milk. After two weeks of treatment his symptoms were greatly improved, and in six weeks all symptoms ex-

cept weakness, which was much less, had been relieved and he was on a diet composed of rare beef, potatoes, wheat bread, and milk. His improvement was rapid from this time. At intervals for four months the treatment was discontinued. He was instructed to return in March for more treatment, as his previous outbreak had occurred in April and it seemed advisable to anticipate, if possible, the likelihood of a recurrence. Although the patient failed to report at this time as requested, he escaped with only a slight erythema of the hands and with no further symptoms of pellagra. Two years later he died of chronic interstitial nephritis under my care.

It is an important fact that in those cases treated with atoxyl there will appear about the anniversary of the original attack a slight erythema, which usually amounts to a simple redness and is accompanied by none of the constitutional symptoms of the disease. At the second anniversary this erythema is absent, as a rule, though recurrences will sometimes occur on the first and second anniversaries without other symptoms. The cause of these outbreaks without other symptoms cannot be found, but it can be said that this condition should not be counted as a true recurrence nor is it of any great significance. It does not indicate any unfavorable state of the patient.

In another place there is a reference to a female patient who received the atoxyl treatment and, though her symptoms were grave with decided mental deterioration, she has made splendid progress. It is a year since the beginning of her affection and she has just had the usual outbreak of erythema without other symptoms. In November when treatment was begun she was in a pitiable condition. The erythema and diarrhea had subsided, but the mental state was very distressing. Her weight was about one hundred pounds. Since that time the improvement has been rapid, and in April she has gained twenty pounds and all the depressive mental symptoms have disappeared. There is no doubt but that she will make eventually a good recovery. The success of the atoxyl treatment in this case was largely due to the co-

operation of the patient. In such cases as this we are almost forced to accept atoxyl as a specific, and in many cases, as mentioned, it seems to have almost as great specific effect as mercury in syphilis. Such results are most encouraging and the observer is forced to admit that there is certainly a degree of specificity in this treatment. Could the drug be administered in a way that would remove the toxicity, no better remedy could be asked for and our discussion would stop at this point. It is to be hoped that some of the untoward results are due to faulty technique. It is known that the atoxyl of the French differs in degree of toxicity from that of the Germans, therefore may we not hope that there are possibilities of the discovery of other errors and variations, the correction of which would give us a safe product?

The fact that the returns from the use of the arylarsonates are often very tardy should be held constantly in mind. Many cases pass from our observation and the clinical record is marked unimproved, but many of these patients subsequently make good recoveries. Reference has been made to such a case. Treatment should not be abandoned because returns are not immediately forthcoming.

Soamin is the trade name for another arylarsonate, which is closely allied chemically to atoxyl. The only difference is said to be in the water of crystallization, but according to E. H. Martin there is five per cent more arsenic in soamin than in atoxyl. There seems to be decided differences regarding the relative arsenic values of these preparations. Lavinder and Babcock[1] state that the percentage of arsenic in soamin is twenty-two and in atoxyl twenty-six. Martin considers soamin as an amino-phenyl-arsonate. In more exact terms it is sodium-para-aminophenylarsonate, having the structural formula $NH_2C_6H_4,ASO(OH)ONa,5H_2O$. This drug has been much used by Babcock, one of the most experienced pellagrologers in the country, and his employment followed a disappointing experience with atoxyl. I have not had occasion to use it up until this time because atoxyl has always accorded such satisfactory returns since I learned how to ad-

[1] Lavinder and Babcock's translation of "La Pellagra," by A. Marie.

minister it and the proper dosage. In the light of Babcock's experience and the favorable report of E. H. Martin of Hot Springs, Arkansas, as well as the difficulty of securing atoxyl in a satisfactory form I have begun the use of soamin, but my results cannot be recorded at this time so that the reference to this drug will be gleaned from the splendid report of Martin. It seems quite probable that soamin is much less toxic than atoxyl. The usual dose of soamin is ten grains, which represents two and a quarter grains of metallic arsenic and is equal to four grains of arsenic trioxide and more than one-half ounce of Fowler's solution, but still no arsenical symptoms are produced by this administration. When given in over dose there will be produced gastric pain but no diarrhea, insomnia, nervousness, dizziness, ataxic gait, a cloudiness of vision, amblyopia, and sometimes optic nerve atrophy. Martin emphasizes the fact that this is not arsenic poisoning and that the arylarsonates are new drugs *in toto* and not merely preparations of arsenic. He says further that it is a question if arsenic is a specific in syphilis, but states as a fact that these preparations certainly are. This observer has used atoxyl extensively, but abandoned it for the less toxic arylarsonates and finally decided that soamin was the safest. In the beginning of his experience with this drug he used it in much larger dose than now thought necessary, but he has never seen a case of amblyopia as a result. He mentions a case in which the patient took the drug without advice after he had given a course of sixty-five grains. The patient added one hundred grains in ten injections so that he received two hundred and sixty-five grains without an interval. One hundred grains is counted the maximum amount for a course and this should be followed by a pause of three weeks, hence it was not surprising that this excessive treatment was followed by optic nerve atrophy. The sight, however, was gradually restored and at the end of six months vision was perfect in one eye and greatly improved in the other. Martin had heard of two other cases in which complete amaurosis was ascribed to the use of soamin, but it was learned that partial atrophy preceded the use of the drug. He has reduced the dose from ten grains

to five grains on alternate days, and as a consequence has had no bad results; but he is careful to have eye examinations when there is the slightest occasion for it. He had under his care eight cases of pronounced pellagra and five suspected cases. The five suspected cases were promptly relieved of the suggestive symptoms by a few injections of soamin. Of the eight pronounced cases only five could be treated; the others were too far advanced. The five made apparent recoveries in a few weeks, but only one case has been kept under observation for more than a year. He employs the anticipatory treatment, which has been found by me to be of such great benefit in the use of atoxyl. The following interesting report of a case treated with soamin speaks well for that remedy:

"The patient was Mrs. J. M. K. of Newton, Alabama, aged 39, white, 6-para, family history good. Had been an inveterate eater of corn bread and still longed for it. Had had indigestion for several years, but no previous diarrhea. She came under my care on July 10, 1910. Four or five months previously she had become listless and moody, and ceased to take interest in anything. Three months before I saw her the eruption appeared on her hands and diarrhea began. She became progressively worse, and when I took the case both arms were in bloody bandages, being denuded from above the elbows to the finger tips. There was a lesion in the right axilla, which had probably been superinduced by trauma, as there was no corresponding lesion in the left axilla, and pellagrous lesions are practically always symmetrical. She had also lesions on both feet and around the anus and vulva. The most remarkable ones were on her face, one covering the entire forehead and another merging into it, covering nose and cheeks and surrounding her nose and mouth.

"She was having on an average ten bowel movements every twenty-four hours. The right pupil was slightly larger, but both reacted to light. Patellar reflexes were normal in the right leg, absent or nearly so in the left. She was rational during the day, but said that she did not feel so when left alone, and she was

delirious every night and could not sleep much. Her temperature ranged from normal to 100° F., but her pulse was usually 120. The tongue and mouth had the usual boiled red appearance, and nourishment had to be forced. She was weak to prostration, and had been way-billed by several physicians to her home and a speedy death; in fact, her father was with difficulty persuaded to allow her to remain a few days to see the result of the first injections, and had she not been really too weak to be moved she would in all probability have been taken on home to die.

"But five days later, after having received three injections of soamin, amounting in all to eight grains, all opposition was waived. An improvement could be noticed in her skin, and the bowel movements were only six or eight per diem.

"After the fifth injection, amounting in all to fourteen grains, her improvement was marked, skin lesions were drying and not seeping as before, and bandages could be left off. Bowel movements five per diem.

"August 1, three weeks after beginning treatment, had had nine injections, amounting to twenty-one grains. There was new epidermis forming on all lesions, some spots entirely covered, bowel movements three per diem.

"August 11, thirty-two days after beginning of treatment, she was able to go home; had had twelve injections, amounting to twenty-seven grains. All lesions were covered with new epidermis and the face was clean. The bowel movements were two daily. She called at my office and weighed seventy-six pounds; ten pounds of this had probably been gained during the month's treatment. Her husband guessed her weight at sixty pounds when treatment was begun. Her average weight when well was one hundred and twenty pounds.

"On September 19, letter stated that the injections of soamin were being continued, two grains every fourth day. She was doing some hand work and could walk a mile without trouble, although the pains in her feet from the old neuritis bothered her greatly.

"October 6, a letter states that improvement continues, but still has pains in feet and head; weighs eighty-five pounds.

"November 7, letter states that patient weighs ninety pounds and eats everything except corn bread, which is not permitted. Digestion good. Can do light housework. Her finger nails have loosened at the roots and are renewing. She still gets the injections, and has now had about sixty-five grains in four months. The treatment will be stopped at one hundred grains, and if it is renewed next spring there is no reason to believe that she will have a relapse."

This patient at Christmas was still in good health and weighed one hundred and three pounds. This case is a fair illustration of what can be done in pellagra if the treatment is persisted in for a long enough time, using caution about the dosage, always having in mind that the ideal treatment consists in giving the largest possible dose without producing toxic symptoms.

When salvarsan appeared it was eagerly sought as a safer and more effective drug in the treatment of pellagra. In my own experience the results have been most discouraging, and I much prefer atoxyl. My cases did not even show temporary relief. Yesterday one of my patients who was given the salvarsan treatment last summer returned with a fresh outbreak. He said that it required several weeks for him to recover from the effects of the treatment last summer. His outbreak this spring was no less severe than formerly. In my opinion he would have been much better off if he had been given the atoxyl. Why salvarsan is not effective I do not know. It may be that in this form of treatment the arsenic effect is not kept up long enough and the amount of arsenic is not so great as in a course of soamin or atoxyl. My colleagues tell me that their experience, too, has been unsatisfactory. Crowell and King have used salvarsan in nineteen cases of pellagra with favorable results in the majority of cases. It is generally accepted that the drug does no good except in those cases with a coincident syphilitic condition.

E. H. Martin summarizes thus:

(1) Soamin will relieve all of the symptoms of most cases of pellagra; it fails only when the condition of the patient is so feeble, complications so severe or the disease so aggressive that it cannot be given in sufficiently large doses. Usually it causes no reaction unless given in over five-grain doses. Some cases would require more and could not stand the reaction from the endotoxins. Given in ordinary doses, it must be kept up for several years, the time yet uncertain. It is probable that if ten-grain doses were safe that there would be no relapse, at least so one physician reports to me.

(2) Salvarsan causes no symptoms if properly given to healthy people. In short, no disease germ, no reaction.

(3) The fever following the administration of salvarsan to a case of syphilis is not due to the drug, but to the endotoxins released from the killed germs; and is both diagnostic and prognostic.

(4) The fever following the administration of salvarsan to a case of pellagra is not due to the drug, but to the endotoxins released from the killed germs; and is also diagnostic and prognostic, and further proves beyond a doubt that pellagra is a parasitic disease caused by a micro-organism vulnerable to "606."

(5) That it is at least reasonable to believe that this organism is a spirochete or a spirillum.

(6) That the character of the reaction, the duration, of the fever especially, shows that the germs of pellagra are located principally in the brain and spinal cord.

(7) The endotoxins released by the destruction of the pellagra germs are so highly toxic to the human host that the dose of the drug must be proportioned in order not to destroy too many micro-organisms at one time, or the results may be disastrous to the patient. Observing patients given large doses of salvarsan, one can readily believe that in some cases a condition paralleling the so-called "congestive chill" in malaria might be produced.

(8) Salvarsan does not cure pellagra in one dose, owing to the invulnerability of the germs at an early stage of development.

(9) Prompt disappearance of symptoms shows that the older germs are killed.

(10) That small and increasing doses, repeated within the time required for the development of the germs from the invulnerable stage to just before the stage of reproduction, gives us a rational treatment of pellagra and should offer as much certainty of a cure as quinine in malaria when properly given with respect to the seventh day.

While these conclusions of Martin are based on a speculation, they are at least suggestive and interesting. The outcome of the present work on etiology which is being pushed in so many quarters will be awaited with added interest by those who share this view.

Favorable results have come from the employment of sodium cacoadylate in the treatment of pellagra. In those cases where atoxyl and soamin cannot be administered because of idiosyncrasy or otherwise it should be considered. When given it should be used in the same dosage as in syphilis, that is, three grains. One strong point in favor of the employment of this drug is the very convenient ampoule in which it is dispensed. I have seen splendid results from the use of this preparation. Its use has not been general enough to make a very definite report.

Arsacetin was employed by Ehrlich as a substitute for atoxyl and soamin. It is the acetyl of atoxyl and is found on the market in the form of a salt.

The solution of the arsenite of iron which is known abroad as Zambeletti's solution has been effective in my hands. It is especially well suited for combination with one of the above-mentioned arsenic preparations. It has been very successfully used on the days intervening between the atoxyl and soamin administrations. As it is administered hypodermically, the objection of Lombroso to the use of iron because it was not well borne by the stomach in pellagra is done away with and a much-needed preparation of iron is found which cannot be harmful. As a rule there is no anemia of any consequence in pellagra, but it will be recalled that a large percentage of pellagrins are infected with hookworm and consequently are in need of iron; in such

cases this preparation is well adapted. The amount of arsenic is comparatively trifling and adds nothing to the value of the preparation. Of course this preparation is not indicated except when anemia is present. It will be found that it is a satisfaction to the patients to have some treatment every day, and this drug fills this bill well. Usually when the victim applies for treatment he is depressed and thinks that the treatment should be formidable in proportion to the gravity of the disease. Deception is not necessary, but it is necessary to make him sufficiently well contented that he will remain under treatment for a sufficiently long time. These patients, especially when they come from a distance and are not confined to bed, are prone to become dissatisfied because of the three or four days between treatments. It is a common occurrence for the patient to leave after one or two treatments, in spite of the fact that he may be beyond the reach at home of a physician who could administer the drug. It is quite a problem to be able to prevent this occurrence.

Fowler's solution and Donovan's solution have been employed in the treatment of pellagra from the first suggestion of the value of arsenic in this disease. There can be no doubt of their efficacy in mild cases where an immediate arsenic impression is not important, but time is too often lost in waiting for the effect. The importance of early treatment cannot be too often nor too much emphasized. For the reason of this tardy action and the fact that both these preparations are too toxic to be given in doses large enough to produce the desired result I consider them a menace to the successful treatment of pellagra. An exception should be made in the case of pellagra in children, where the drugs seem to do some good, but it must be taken into consideration that pellagra in children is usually a trivial disease. Pellagra cannot be cured by either of these preparations of arsenic, but both may disturb a digestion which is already badly deranged. It is wisest to consider both drugs contraindicated and to begin no treatment until the hypodermic plan can be instituted.

No phase of the treatment of pellagra is so important as the diet. This matter has never received the attention which its

importance deserves. We note that Manson [1] strongly emphasizes the importance of diet in sprue above every other consideration. It has been noted on another page that there is a strong similarity between pellagra and sprue. The treatment of diarrhea and stomatitis form the greatest difficulty in the treatment of pellagra just as in sprue. It has been impressed on me repeatedly that absolute rest and a strict milk diet would do great good in pellagra, just as in sprue. Certainly rest in bed is the best way to conserve the little strength of the cachectic patient, and it also has a most pleasing effect on the diarrhea. In sprue Manson directs that the patient take the milk very slowly through a straw or from an infant's feeding bottle. In the beginning sixty ounces is the limit of the amount of milk allowed in twenty-four hours. This would be too large an amount in the beginning in pellagra. Manson increases this amount until one hundred ounces are taken. All other forms of food are withheld and the patient is kept on this diet for six weeks after the mouth heals and the stools become solid. This plan with slight modifications is the best for pellagra. As the stomach is usually affected and there is decided anorexia, it is well to begin with not more than a pint in the twenty-four hours and increase one ounce with each feeding until a sufficient amount is taken to supply the number of calories needed. It should be remembered that many pellagrins go for weeks with practically no food. It is unfortunate that so few of our patients among the rural population of the southern states will take milk. It would be well if the next generation would learn to take milk and to depend on it more largely than at present. If all our patients could be induced to take milk the problem of the treatment of pellagra would be greatly simplified, as it will be found that this diet is as effective in pellagra as in sprue. The extreme irritation and sensitiveness of the mouth causes the milk to be especially grateful. If it cannot be taken, it is well to try buttermilk. Taylor of Columbia has suggested the use of the Bulgarian bacillus in the milk. After the milk has been taken for some

[1] Manson, Sir P., "Tropical Disease," 1907. Also in Allbutt's "System of Medicine." 1905.

time and is well borne, a raw egg may be added to it, beating the two together thoroughly. The nutrition of the patient is a matter of as great importance as in tuberculosis and there can be no better food for this purpose than milk. If large tough curds appear in the stools it is advisable to resort to peptonization, reducing the length of time of the process gradually. Manson advocates the use of fruit juices in sprue; I have not yet tried this plan in pellagra. If milk in all its forms fails it is well to resort to a broth composed of a meat, as beef, mutton, or chicken, and a cereal, as barley, rice, or oatmeal. It is well to prepare the meat broth and the cereal broth separately and mix the two at the time of using. It is also well to vary the diet day by day by a rotation in the kind of broth so that the patient will not tire. It is important not to depend on this diet but a short time, as it is not sufficient and the patient will lose weight on it, even though the attack is subsiding. As soon as the diarrhea subsides it is well to begin with the regulation semi-solid diet. Often a patient who cannot or will not take milk will take milk toast, and it forms a very suitable food. Later rare beef, white potatoes, dry toast, and foods of this class are in order. It has been my rule to withhold all vegetable and fruit food until the symptoms have all subsided. As the disease usually appears in the spring, it is important to warn the patient against the use of all new vegetables and early fruits, as strawberries.

It is customary to instruct the pellagrin not to eat corn food in any form, but so many of my patients have never eaten this form of food that this advice is often superfluous. In others who are sceptical about the connecting of this much-abused American cereal with the etiology, this advice is ignored and I have never been able to see that they fared any differently from the patient who never ate maize at all. It is still a routine thing to advise that no corn be eaten, and will be until a definite conclusion is reached regarding the true cause of the disease.

When vomiting is troublesome or in those cases in which it is impossible to get the patient to take food it is often helpful to resort to proctoclysis, using normal saline solution. Some ob-

servers have advocated this as a curative measure of decided benefit, but the yearly recurrence in most cases has soon dispelled this idea. This plan will usually fail if the rectal tenesmus is marked.

Alcohol or some of the proprietary foods composed chiefly of alcohol have been used, but in my experience have proven harmful, and there seems a definite contraindication to the use of any form of drug or food of this class.

For the diarrhea I have tried a preparation described by Tennenbaum [1] under the name "almateina." It is a synthetic product, claimed by the chemist Lepetit to be produced by the action of formaldehyde on hæmatoxylon. It occurs in a fine powder of a dark red color. It is given in doses of seven and a half grains (0.5 grams) every three or four hours. This drug is claimed to relieve many forms of diarrhea, but in this disease it has not been uniformly successful. Some of my colleagues have reported favorable results from its use, but the number is not large. There is no drug in the Pharmacopeia that will relieve the diarrhea of pellagra. Any attempt to produce such a result always results in failure and usually the measure is otherwise hurtful to the patient. It would be well if the use of so much bismuth was abandoned, as it never does good, and an impure preparation theoretically would be contraindicated, especially in pellagra, on account of the mouth condition. Until the underlying condition is relieved or subsides nothing will benefit the diarrhea or the stomatitis. For the stomatitis simple cleanliness is the best plan of treatment. This may be supplemented with some simple astringent, if desired, and in some cases a dilute solution of peroxide of hydrogen may be used as a mouth wash. A. E. Alford of Greensboro, North Carolina, has told me of his success in the use of such silver salts as argyrol, both on the skin lesions and by mouth, for the stomatitis and gastro-intestinal condition. This would deserve further trial.

For the skin lesions I have never found an application that would do any good. The condition may well be compared to the

[1] Tennenbaum, H., "Ein verlaessliches Antidiarrhoillum." Zentralb. für innere Med., 1909.

skin lesion of small-pox, which will subside at a certain time, regardless of, or in spite of, treatment. In small-pox all that can be done is to protect the skin and keep it in good hygienic condition. So also in pellagra after the use of sufficient soap of a bland character and warm water followed by a simple protecting unguent, as petrolatum or lanolin, all that is possible has been done. Babcock recommends the following:

Pulv. calamine	4 drams	Rose water	2 ounces
Pulv. zinc oxide	3 drams	Lime water to make ..	1 pint

This is to be applied freely at short intervals. This same observer also employs the following:

Pulv. calamine	½ dram	Olive oil	½ dram
Zinc oxide	½ dram	Lanolin to make	1 ounce

It is important to consider the sleeplessness and nervous irritability which exhausts so many patients. For these conditions such drugs as trional and veronal, as well as chloral and paraldehyde, have been employed. I have been especially successful with chloretone, which has the great advantage of being sedative to the stomach in cases of nausea and vomiting.

For the pain of a lancinating character Niles recommends five-grain doses of acetylsalicylic acid four times a day. For the severe pains in the hands and feet I have never found any remedy. Even opiates are very unsatisfactory.

It was hoped that transfusion would be the great remedy in the treatment of pellagra. After a thorough trial the results are rather discouraging. I have seen it done twice: once by T. M. Green of Wilmington, North Carolina, and once by J. W. Long of Greensboro, North Carolina. In both instances the recipient was in an extreme condition and the donor was a healed pellagrin. Both donors were poor subjects, but were the best at hand. One of these, at least, was heavily infected with hookworm and the hemoglobin was quite low. The other was not much better. In both cases death followed in the course of about the same time that we would otherwise have expected.

H. P. Cole and G. J. Winthrop of Mobile have done quite a number of transfusions and their results have been more encouraging. Their conclusions were as follows:

(1) Transfusion offers a means of combating the anemia, stimulating the recuperative functions and perhaps of furnishing antitoxic substances to pellagrins.

(2) The lessened mortality and marked improvement in transfused pellagrins leads us to anticipate the establishment of a serum therapy in the disease.

(3) Transfusion may be offered as a surgical therapeutic procedure in pellagrous cases, pending the perfection of a successful serum therapy.

These observers were working on the assumption of the correctness of such authorities as Antonini and Mariani, who claimed that a definite immunity is developed in a healed pellagrin and that the serum has a definite antitoxic action against maize poisoning. Cole and Winthrop then conclude thus:

(1) Pellagra is an intoxication.

(2) The toxic principles of pellagra exist in the blood of pellagrins and will produce pellagrous symptoms when transferred to other animals.

(3) Pellagrous serum exhibits definite precipitative, hemolytic, and antitoxic properties.

(4) An artificial immunity can be produced in animals and exists in cured pellagrins.

All of this work is based on an assumption that damaged maize causes pellagra. This is not generally accepted, and since I began this work the number who reject the theory has greatly increased. Until this problem of the cause is determined, little work of this kind can be done along this line. In the meanwhile blood transfusion is empirically indicated when other measures have proven ineffective and when a suitable donor can be had. A suitable donor may be had from the non-pellagrous as well as from the pellagrous. Recent work has shown that a previous history of pellagra does not render an individual a more desirable donor than otherwise. This would tend to show that there is

not that specificity of the blood serum which has been supposed to exist.

Hydrotherapy has been stressed by various writers on pellagra and it is probably of some service, especially as a placebo when it can be administered in an institution especially equipped for the purpose, employing trained attendants. Unless given with great care and particular attention to the individual condition of the patient, there would be a definite contra-indication. For my own part I would prefer the salt bath or rub, especially in the neurasthenic type of the disease. This rub is very simple, and may be given anywhere without the necessity of going to an institution. It must be considered in advising any general line of treatment that the large majority of these patients live in the country and are usually poor, hence treatment must as far as possible be adapted to the conditions, for the reason that, like syphilis, pellagra requires about three years of treatment before the patient can be safely discharged. In some cases in which the restlessness is very marked the hot bath cautiously given will prove sedative. The cold bath should be given with unusual caution. Medicated baths, chiefly of arsenic and sulphur, have been tried, but no very signal improvement has been recorded from this plan of treatment. The special indication in this latter plan is certain conditions of the skin and also in intestinal conditions more particularly when attended with marked wasting.

Much attention should be paid to the general hygienic conditions. While pellagra may occur in the most robust and the best nourished, it is a well recognized fact that it finds a most favorable soil in debilitated people of all ages. It has been mentioned that the presence of hookworm disease is a predisposing cause and that the eradication of this condition will largely relieve the pellagra situation. It must be held in mind that this is only one of the predisposing causes which may be treated. Pellagra occurs many times among the better classes, who would never be suspected of living in anything but a good hygienic condition. This is especially true of old people living alone. They often pay too little attention to their nourishment and in

some instances unconsciously become dependent on alcoholic stimulation. In my judgment alcohol is the most constant single predisposing factor in pellagra and many of the so-called cases of pseudo-pellagra attributed to alcoholism are really pellagra. I recently saw by accident an old gentleman in good circumstances who was nursing sore hands and who had suffered for a long time with diarrhea. His mental condition was counted an infirmity of advancing years. He was not a consumer of maize, but he had a typical case of pellagra. A general debilitated condition predisposed to this trouble and more attention to his personal hygiene and diet might have given him the resistance needed to combat the disease.

Change of climate in pellagra will do fully as much as in tuberculosis. In time it will be generally recognized as important as in tuberculosis. As a rule cooler climates with short hot seasons and long winters are thought to be beneficial. Bass reported twelve cases sent to a cool climate and Niles had four cases treated the same. In all the improvement was quite marked as well as prompt. Bass suggests the use of an artificially refrigerated ward for the purpose. In my experience it is not altogether the cool climate which does the good, but also the general effects of a change of any radical kind, though I recall the fact that in many travels through the mountains of North Carolina I never encountered a case of pellagra, in spite of the fact that a constant search was made. Cases of pellagra have occurred in Asheville, but as a rule they were sporadic and were brought in from a distance. In some instances the seashore is of decided benefit, but the essential thing is to have a radical change. It is a notable fact that cases of pellagra sent from the South where there was no improvement secured will often make the most rapid and marked improvement in the institutions of the North, even though no special line of treatment is instituted. I have known patients advanced to the point of decided mental change to be entirely relieved in a few weeks in such an institution. This improvement is always indicated by a rapid gain in weight. This gain in weight, as previously mentioned, is as

important as it is in tuberculosis and is as reliable an indicator of the improvement. As long as a pellagrin gains weight the case is to be counted on the improvement side of the scale.

In no class of cases does kindly encouragement mean so much. If the patient knows the nature of the disease he should be told how many recoveries are being made and should be given the impression that it is only a question of how long it will require to effect a cure and how coöperative he will be. These patients will try the patience of the most long-suffering with their hypochondriacal manifestations, but there is no class of cases who are so grateful for help, and they will invariably "return to give thanks." Certainly no class of people will appeal so strongly to the humane medical man as the pellagrin, for in no disease is there found such a picture of abject despair.

While the progress in the treatment of pellagra has been slow and there remains much to be desired, a consideration of the old Italian literature is sufficient to prove that much progress has been made. Until only a few years ago all writers stated positively that it was a hopelessly incurable disease and that all remedies were equally unavailing. It is interesting to read the difficulties encountered by Gaetano Strombio, the greatest of all pellagrologers, in his efforts to find a cure. He tried a remedy which he had introduced for the treatment of elephantiasis and leprosy in pellagra. This remedy was a snake broth! He also used Spanish fly with no result. As he found all remedies tried by him to be without result, he went to celebrated physicians of the time for help and advice. One advised the plan of one Doctor Galli, which consisted in the use every morning of the juice of water cress, to which was added one ounce of honey and a small amount of the pulverized eyes of the lobster; to this was added a little arnica mixed with spirits of ammonia. The diet was advised to be entirely animal, and everything that would create acid was to be avoided. Balserei, another to whom Strombio applied for advice, had never had any experience, but advised turpentine oil to bring up the nerve strength, and he also recommended pine shoots macerated and used for the bath. Odoardi

was said to have been successful with powdered whole lizards. Strombio considered the seat of the disease to be the abdomen, and therefore resorted to the use of purgatives to remove the impurities. He also used koumiss, rhubarb, and tamarinds, and hoped to reduce the number of stools.

Pellagra can no longer be counted among the incurable maladies. There is as much hope of success in its treatment as in many other diseases which are counted far less malignant. It is not a self-limited disease, and unless vigorously treated from the beginning the same result must be expected as in improperly treated syphilis. The therapeutic nihilist has no more right to treat pellagra than to treat syphilis.

Finally the fact must be emphasized that the most successful treatment of pellagra consists in the early diagnosis.

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